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EPIDEMIOLOGY OF TUBERCULOSIS[1,2]

Principles of Programs of Tuberculosis Associations

EDWARD S. GODFREY, JR.

While the epidemiologist from time to time seems to be indulging in merely satisfying the insatiable curiosity that is properly a part of his nature, his real function is to provide the scientific basis for sound health legislation and administration. It is his function to bring together the findings of the clinician, the laboratory worker and investigators of the environment, and from them to evolve a logical program for the control of a given disease. It is his further function to discover promising clues whose follow-up may lead to a betterment of existing practice. He has other functions, among them the collecting, as well as the assembling, of facts needed to establish a working hypothesis. He is an inventor rather than a physicist or a manufacturer, though he, like the inventor, may be all three.

The scientific basis for a program for the control of tuberculosis was set forth three years ago by one of the most outstanding epidemiologists of our time, Dr. Wade Hampton Frost. This paper was published in the Journal of the American Public Health Association for August, 1937. As a scholarly appraisal of the factors involved and as an example of cogent reasoning and of concise statement, it will stand as a landmark in the history of the tuberculosis movement. Doctor Frost pointed out that "for the eventual eradication of the tubercle bacillus, it is not necessary that transmission (of the tubercle bacillus) be *immediately* and *completely* prevented." That "it is only necessary that the rate of transmission be held permanently below the level at which a given number of infection spreading (that is, 'open') cases succeed in establishing an equivalent number to carry on the succession." This rate of transmission is what determines the "biological balance" to which Doctor Frost later referred and which he believed we were warranted in

[1] Presented at a session of the Administrative Section at the 36th annual meeting of the National Tuberculosis Association, Cleveland, Ohio, June 3, 1940.

[2] From the State Department of Health, Albany, New York.

inferring had been turned in favor of the human host and against the tubercle bacillus.

This biological balance is what determines the rise and fall of our acute epidemics. In some diseases such as influenza and measles it is wholly or almost wholly dependent upon nature herself. In others, as in typhoid fever and in diphtheria, man may play the dominant rôle. In tuberculosis, I agree with Doctor Frost again that there are "sound reasons for doubting that the general and rapid decline of tuberculosis during the last fifty years has been due *principally* to the measures which have been taken for the specific purpose of preventing infection." This does not mean, however, that they have not been of material aid, nor that specific measures may not assume the dominant rôle in hastening the day when tuberculosis will cease to be an important medical and social problem. This will require that additional resources be provided, that the experience of the past be studied and our efforts directed as that experience dictates.

The great significance of Doctor Frost's paper is to be found in a projection of the trend line of tuberculosis mortality in this country from 1920 to 1938. This indicates that if there should be no change in the susceptibility of the human host and no change in the adaptability of the tubercle bacillus and, I may add, no slackening in our efforts, fifty years from now the tuberculosis mortality of the United States will be about 5.5 per 100,000. This means its virtual eradication in some parts of the country to balance higher rates in others.

It is my opinion that this rate of decline can be materially accelerated if the specific measures assume the *dominant* rôle. Society can do this by providing the necessary hospital beds to isolate the open cases of tuberculosis, render them noninfectious in many instances or in any event so instruct them that they are unlikely to be the promiscuous spreaders of infection that they were before they entered the institution, by providing the necessary field, clinic and nursing services and by dealing with tuberculosis as a communicable disease.

There should be a better distribution of available beds, adjusted to the needs of the area rather than its willingness or capacity to pay for their construction and upkeep.

There must be a different philosophy guiding the operation of sanatoria so that *per diem* cost per patient is not the first consideration in judging its efficiency. This calls for a better understanding of the purpose of a tuberculosis hospital on the part of taxpayers, appropriating bodies and even many hospital superintendents. These institutions are

only a part, though a necessary part, of the whole program intended to make most or all of them unnecessary as tuberculosis hospitals. In consequence the buildings and the layout must be so designed as to suit some other useful purpose in the future.

I think the time has come when we should consider the establishment of, or the adaptation of, certain existing institutions for the care of the vagrant and recalcitrant type of patient. There is no need to tell of the demoralizing effect of such a patient in an institution where the other patients are anxious to recover and are conforming to the prescribed regimen. To discharge recalcitrant open cases violates every concept of the proper control of a communicable disease. We would not do this with a known case of smallpox.

Along with a consideration of the distribution of tuberculosis hospital facilities must go a study of the adaptation of existing hospitals and sanatoria to a better purpose and lessened expense. Many of these are quite suitable for custodial care though they fall far short of our modern concept of what is needed for remediable cases. There are psychological factors which must be thought of in any such differentiation. It is not a simple matter and apparently needs deeper study than has yet been given to it.

The tuberculosis hospital serves a dual purpose: first, segregation; second, treatment looking to the arrest of the disease and the rehabilitation of the patient. In our enthusiasm for the second purpose, I have the impression the first is getting too little attention. Granting the necessity of maintaining a hopeful attitude on the part of remediable patients, must we not look at the relative costs and examine the actual results of remedial care from the standpoints both of physical condition and opportunities for subsequent employment? Industrial compensation laws, while a great social advance, sometimes operate to the disadvantage of the person known to have had tuberculosis.

The distribution of hospital beds and the adjustment of existing facilities will require the aid of both state and federal governments if the need for them rather than the capacity to erect and maintain them is kept as the primary consideration. The state may aid as in upstate New York by establishing and operating regional hospitals charging the cost of the treated patients to the county of established residence. The expense of the field clinics of the hospital is borne by the state. The public health nursing services are provided by the counties with state aid and by any cities from their own resources.

It is my opinion that state-operated institutions will prove more

satisfactory than state grants-in-aid to local institutions. There are a number of reasons for this belief but the important ones are that serving larger areas they can be staffed by better trained personnel, can be located to serve not only the immediate need for tuberculosis care but for future uses as well, and if they are operated under state health departments, as they should be, there is a better coördination of the hospital staff with other facilities of the health department.

The federal government should—no, must—assist the state and local governments in carrying out this work. In many sections of the country where the need is greatest, the provisions for meeting it are least, and apparently cannot be met out of local resources. Furthermore, federal guidance in the best use of resources is highly desirable. Note that I say guidance which does not mean dictation, coërcion and a variety of other opprobrious terms used to frighten people. A high prevalence of tuberculosis in one section of our country is in some measure a menace to every other. If needs are better met at home there is less tendency to travel either to obtain care at some other state's expense, or for a supposed benefit of climate.

The itinerant cases seem rather obviously to be the concern of the federal government, so that they may not be left to spread infection among their fellows while a search is made to find the community responsible for the cost of their care. Federal assistance in research needs to be continued and amplified, particularly in field studies involving more than one state, perhaps covering considerable areas of the country.

Needless to say that the federal assistance now given under the Social Security Act should be continued. The assistance given to the basic structures of our state and local health departments is essential to any complete program for the control of tuberculosis. Without the field staff of a health department actively interested in case-finding, a tuberculosis hospital is just another specialized hospital. Its importance as an element in solving a community health problem is likely to be lost in details of treatment and internal administration. The Social Security Act enables the employment of more personnel, medical, nursing and clerical, to implement case-finding and the other extramural activities. It is these activities in particular which must be better developed and better directed if our specific measures are to assume the dominant rôle in pushing down the declining death rate.

First of all there should be a better allocation of deaths to the places where the decedents developed their disease. Certain states have very

high recorded death rates because they are health resorts for the tuberculous. Within states many counties have high recorded rates because a state or regional tuberculosis hospital or a hospital for the insane exists inside their borders. In certain states efforts are made to correct these distortions by allocating deaths to the place of former residence.

This has been attempted in New York State, but I doubt it has achieved complete success because of the continued excessively high rate reported each year for Sullivan County. This county became noted as a tuberculosis health resort many years ago when Loomis Sanatorium opened. Suspecting that many of the tuberculosis deaths allocated to this county belonged elsewhere, a study was made of all tuberculosis deaths occurring in the years 1930–33 inclusive and the first eight

TABLE 1

Deaths and death rates per 100,000 population from tuberculosis (all forms) in Sullivan County; death rates in New York State (exclusive of New York City), 1930–1933

YEAR	SULLIVAN COUNTY						NEW YORK STATE (EXCLUSIVE OF NEW YORK CITY) DEATH RATE
	Recorded Deaths		Resident Deaths		"Corrected" Resident Deaths		
	Number	Rate	Number	Rate	Number	Rate	
1930	130	371.2	26	74.2	13	37.1	59.5
1931	122	358.6	30	88.2	16	47.0	54.6
1932	90	272.6	23	69.7	13	39.4	51.1
1933	99	309.2	40	124.9	22	68.7	46.9
1934*			22*	106.4	11*	53.2	

* Eight months only.

months of 1934. The results are shown in table 1. The study was carried out by Miss Elsie Dochterman, who was Research Assistant in Epidemiology at the DeLamar Institute of Public Health, Columbia University, at the time.

It will be seen that while the Division of Vital Statistics allocated 278 deaths recorded in this county to other places, closer investigation discovered 55 others in this period which were not indigenous. Out of 141 deaths classed as resident deaths by the Vital Statistics Division in the period 1930–35, 66 were found to have been improperly allocated to the county. In 62 instances the duration of illness was longer or the duration of residence shorter than stated on the death certificate. In 23 of these both were incorrectly stated.

The health officer should know the facts about persons dying from

tuberculosis in his jurisdiction preferably long before they die. If not previously known, they should be ascertained promptly after death as we would do were it an acute infectious disease. Errors found on the death certificates could then be reported to the proper registration officials. From an epidemiological standpoint we must be interested in the accuracy of our statistics in items relating to time and place, as well as cause, of death. From them we draw certain inferences and formulate plans and we need them to measure the results of our efforts.

Every death report of a previously unknown case is the beginning point for an investigation of a family just as though it were a new case report. And here, with each newly discovered case, is where a real job needs to be done. Too often the criteria of performance on the part of nurses assigned to this work have been based on the number of visits made to the patient or the household. The effectiveness of these visits is not subjected to proper scrutiny. The first objective of the investigation, as in other communicable diseases, should be to discover the source of infection and stop further spread; the second, to find out who have been contacts while the patient has been in an infective stage, and ascertain whether any have acquired the disease.

The first of these objectives appears to have received far less attention than the second. I think there are two reasons for it. One, because of a preference for treating patients who have a chance to recover rather than to house patients for the sake of preventing further spread of the disease. I have a feeling that the campaign for early diagnosis has been construed to mean the diagnosis of *early* cases. It should mean the early diagnosis of all existing cases. The early diagnosis of a late case that is spreading tubercle bacilli under the guise of having asthma or chronic bronchitis is more important than treating a minimal case that is noninfectious. That we are not finding these spreaders is evident from the wide dissemination of the tubercle bacillus, the frequency of appearance of active sporadic cases and the small percentage of older household contacts who are examined.

The second reason lies in the unsuitability of certain criteria as to what constitutes a "good case-finding job." If a certain percentage of minimal cases are discovered and a certain percentage of contacts are examined, the job is classified as good. Like other criteria of this sort, the attainment of some such artificial goal satisfies those responsible for the work. Until all of the members of a tuberculous household over twenty-five years of age have been examined, there should be no criterion

of percentage of minimal cases discovered. Percentages of contacts examined should be judged according to the ages of those examined.

When the records of 17 counties in New York were analyzed a few years ago, it was clearly shown that the contacts below fifteen years of age were examined in much larger proportions than those over that age. At ages over forty less than a fifth were examined. Table 2 shows the details.

A companion table (table 3) shows the yield in cases discovered by corresponding age groups. The higher yields are what we might expect from a look at the age distribution of tuberculosis deaths. The higher

TABLE 2

Household contacts of pulmonary tuberculosis cases and number and per cent of such contacts examined by age groups in 17 counties of upstate New York January 1, 1937–June 30, 1938

AGE GROUP	TOTAL	EXAMINED	
		Number	Per cent
All ages	11,742*	4,159†	35.4
0–4	583	276	47.3
5–9	1,140	633	55.5
10–14	1,545	784	50.7
15–19	1,471	645	43.8
20–24	1,341	474	35.3
25–29	988	337	34.1
30–39	1,339	462	34.5
40–49	1,042	275	26.4
50–59	839	174	20.7
60–69	422	55	13.0
70 and over	203	18	8.9

* Includes 829 contacts for whom age was not reported.

† Includes 26 contacts for whom age was not reported.

age groups are where the cases are found and it is among these that we are examining fewest. Since those examined were all contacts of a previously known case, there is much more likelihood that cases over forty were the sources of the infection of younger cases than secondary to younger cases. It would be interesting to pursue this sort of inquiry further and ascertain the number of open cases discovered in each age period.

When classified by age and sex the low percentage of adult males examined is apparent. Yet the male death rate by age continues to ascend to sixty-five years and is therefore the important group to examine (table 4).

It is easy to get school children to attend a clinic. They have no jobs for which they fear, no home responsibilities, they make the clinic a busy

TABLE 3

Number of household contacts of pulmonary tuberculosis cases examined, cases discovered and case rate per 1,000. Contacts examined, by age groups, in 17 counties of upstate New York January 1, 1937–June 30, 1938

AGE GROUP	CONTACTS EXAMINED	CASES DISCOVERED	CASE RATE PER 1,000 CONTACTS EXAMINED
All ages	4,159	187	45
0–4	276	2	7
5–9	633	4	6
10–14	784	10	13
15–19	645	30	47
20–24	474	45	95
25–29	337	22	65
30–39	462	26	56
40–49	275	24	87
50–59	174	12	69
60 and over	73	9	123
Not reported	26	3	*
Under 15	1,693	16	9
15 & over	2,440	168	69

* Rate not shown. Base too small.

TABLE 4

Contacts of 3,558 cases of pulmonary tuberculosis in four state tuberculosis hospital districts*

By age, sex and examination status as of April 15, 1940

AGE	BOTH SEXES			MALE			FEMALE		
	Number of Contacts	Examined		Number of Contacts	Examined		Number of Contacts	Examined	
		Number	Per cent		Number	Per cent		Number	Per cent
All ages	10,998	5,314	48.3	5,561	2,478	44.6	5,437	2,836	52.2
0–1	62	27	43.5	34	17	50.0	28	10	35.7
2–14	2,352	1,644	69.9	1,172	798	68.1	1,180	846	71.7
15–24	2,385	1,480	62.1	1,216	714	58.7	1,169	766	65.5
25–44	3,206	1,313	41.0	1,668	599	35.9	1,538	714	46.4
45–59	1,883	646	34.3	880	249	28.3	1,003	397	39.6
60+	1,110	204	18.4	591	101	17.1	519	103	19.8

* Duplicate contacts were counted only once.

looking place and help the attendance record. Getting older people to attend is more difficult. Both age and the disease tend to recalcitrancy

to say nothing of the implications the father or mother of a family foresees if either should be found to have the disease.

But these are phases to be studied and means devised to overcome discovered difficulties. The path to the sanatorium must be made easy for the patient and his family. The social investigation should have this as its primary function and not be a search for resources to be exhausted before the community assumes the cost. The great majority of cases come from families in the low income groups with little if any savings. Treatment is expensive even in the early stages. Insistence upon the use of all the family resources means impoverishment of the family. They then become community charges for rent, food and cloth-

TABLE 5

Contacts of 181 cases of pulmonary tuberculosis in Jefferson County, by age groups, sex, and examination status as of February 29, 1940*

AGE GROUPS	BOTH SEXES			MALE			FEMALE			SEX NOT STATED	
	Number	Examined		Number	Examined		Number	Examined		Number	Number examined
		Number	Per cent		Number	Per cent		Number	Per cent		
Total	664	521	78.5	320	248	77.5	324	257	79.3	20	16
0–1	11	4	89.7	4	1	95.0	7	3	85.2	—	—
2–14	173	161		96	94		74	66		3	1
15–24	143	131	91.6	64	56	87.5	72	70	97.2	7	5
25–44	185	141	76.2	88	61	69.3	90	73	81.1	7	7
45–59	92	62	67.4	37	22	59.5	52	37	71.2	3	3
60 and over	60	22	36.7	31	14	45.2	29	8	27.6	—	—

* Ten of these cases had duplicate contacts who were counted only once in tabulation.

ing. A family is wrecked. The prospect of this is one of the chief deterrents to early hospitalization and to continued stay until the disease has been arrested.

Another phase of the kind of persons examined at clinics needs examination. Horton (in a paper to be published) has found from his experience in the clinics held in the area served by the Homer Folks Hospital that:

(*1*) Practically all cases were found at the first examination.

(*2*) The age group eighteen to thirty-five accounted for the majority. Some older ones were discovered through the search for source cases.

(*3*) It was extremely uncommon to discover evidence of pulmonary

tuberculosis in a person who had had a previous negative chest X-ray film at age thirty or over.

The first and last of these observations are of great importance and, if borne out by more extensive observations, indicate that clinic loads can be greatly lightened. The time and effort of the staff can then be devoted to a more concentrated effort among those groups where experience has taught us, tuberculosis is most likely to be found.

The promiscuous tuberculin testing of school children has not been mentioned. I do so only to condemn it as a waste of time, money and effort—at least until the real job has been done. Mass surveys of whatever type must be carefully considered from the standpoint of costs and probable yield. Except for exploratory purposes, they should not interfere with a thorough search among the household contacts.

SUMMARY

Although a biological balance has apparently been turned against the tubercle bacillus, it is doubtful that the specific measures for its prevention have been in the main responsible. It is believed that these specific measures can be made the dominant factor in the further decline of the death rate, and that if it be done intensively, the time when tuberculosis will cease to be an important medical and social problem can probably be reduced by one-half or more. The requirements are:

Ample provision of hospital beds.

Reducing the economic difficulties which so frequently deter active open cases from entering a hospital.

Provision for recalcitrant open cases.

Better localization of the problem, through more accurate death certificates, as to the duration of the illness and the duration of the residence of the decedent.

More thorough investigation of the household contacts, including visiting relatives and domestics, primarily for sources of infection and the segregation or other adequate control of open cases.

A careful consideration of the probable yield from any mass survey, so as to avoid waste of time, effort and money.

Careful record keeping so that results can be measured and unproductive activities can be discontinued.

Tuberculosis is an infectious, communicable disease. It is spread almost entirely by persons with pulmonary tuberculosis who are coughing up sputum containing the tubercle bacillus. Until these people have been found and cared for, the real job has not been done.

CHRONIC COR PULMONALE[1,2]

Its Relation to Pulmonary Tuberculosis

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INTRODUCTION

Chronic *cor pulmonale*, or hypertrophy of the right side of the heart which may or may not be associated with failure, has been relatively neglected in the medical literature and only recently has the scope of its many manifestations, both clinical and pathological, been more appreciated. We are concerned here primarily with chronic *cor pulmonale*; however, we shall first discuss briefly the acute and subacute types.

Acute *cor pulmonale*, unless it is secondary to disease of the left side of the heart, is most frequently caused by a large pulmonary embolus. White (1) reëmphasized the importance of this syndrome in 1935. In cases of large emboli which result in acute dilatation of the right side of the heart without hypertrophy, the onset is usually sudden, cyanosis is marked and the blood pressure is low. Dilatation of the pulmonary artery and conus may be demonstrated by roentgen ray or by physical signs. The presence of shock may modify the presenting signs, especially those of increased venous pressure. Gibbon *et al.* (2) have shown that in cats at least 60 per cent of the blood-flow through the pulmonary artery must be cut off in order to provoke acute *cor pulmonale*. However, because of the presence of reflex factors, an analogy cannot necessarily be drawn in man. Brill (3) has pointed out that acute *cor pulmonale* must be differentiated from acute coronary occlusion, spontaneous pneumothorax and massive collapse.

Whether subacute *cor pulmonale* should be specified as a separate division of *cor pulmonale* is debatable. At times, multiple pulmonary emboli with resultant thromboses and later further pulmonary emboli may have a subacute course (4). Brill (5) has designated subacute *cor pulmonale* as the result of plugging of the lymphatics of the lung with

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[2] This paper was presented in part before the California Tuberculosis Association, Santa Barbara, California, April 12, 1940.

metastatic carcinoma which often originates in the stomach. This plugging causes irritation about the contiguous pulmonary arterioles with formation of small thrombi and resultant hypertension in the pulmonary circulation.

Aetiology of chronic cor pulmonale: Chronic *cor pulmonale* may be divided into primary and secondary types. The secondary type is more common and is caused by any condition resulting in left-sided heart failure which by further back pressure involves also the right side of the heart. Cardiac changes (such as aortic insufficiency, mitral stenosis, aortic stenosis, coronary disease and even beri-beri) are among the main causes. The primary type of chronic *cor pulmonale* may be due either to changes in the vascular arterial system of the lung or to wide-spread alterations in the pulmonary parenchyma and the thoracic cage. Primary vascular changes as a cause of primary chronic *cor pulmonale* are rare. Brenner (6) has outlined in great detail the pathological alterations which may occur in the pulmonary artery. Thromboses of the small arterioles secondary to sickle-cell anaemia (7), primary arteriosclerosis (8) and necrotizing arteritis (9) have also been cited in the literature. The causes of primary chronic *cor pulmonale* due to changes in the pulmonary parenchyma embrace a wide variety of diseases. These include bronchiectasis, silicosis, bronchogenic carcinoma or any disease which by its wide-spread involvement and its chronicity compresses enough of the pulmonary arterial bed to cause this condition.

Our purpose is to discuss here the diagnosis of chronic *cor pulmonale* before and after failure. It is of fundamental importance to know the components of the perfect pathological background for the development of this condition and we shall elaborate on these components especially as they apply to tuberculosis and indicate those which in our opinion are of major importance.

Tuberculosis is only infrequently a cause of chronic *cor pulmonale.* In the Los Angeles General Hospital, Griggs *et al.* (10) observed right ventricular hypertrophy (the right ventricle measuring 0.5 cm. or more) in 4.6 per cent of 1,655 cases of tuberculosis. They stated, "We were unable to correlate the cardiac hypertrophy with specific types of tuberculosis, although, of course, it was generally found in advanced cases." We cannot agree with Nemet *et al.* (11) who reported hypertrophy of the right side of the heart in 33 per cent of their series of 71 cases of tuberculosis. Hirsch (12) stated that patients with rapidly progressing tuberculosis do not have time to develop hypertrophy of the right side of the

heart with or without failure, and he further concluded that this syndrome is most liable to develop in patients who have tuberculosis of the chronic productive type with secondary emphysema and obliterative pleuritis. He found that 33 per cent of 120 patients had some evidence of right-sided hypertrophy, but he did not state whether any of these patients had other cardiac complications which might also have produced the hypertrophy. In a postmortem study of 6,210 cases at the Cleveland City Hospital, Scott *et al.* (13) found only 3 cases of tuberculosis and emphysema with marked hypertrophy and failure of the right side of the heart. They did not state how many cases of tuberculosis were in this group, what type of disease occurred, nor in how many cases chronic *cor pulmonale* without failure was observed. However, it is their opinion that this condition is rare in uncomplicated pulmonary tuberculosis (14).

Diagnosis: The diagnosis of the primary type of chronic *cor pulmonale* in its relation to tuberculosis depends upon the demonstration of enlargement of the pulmonary artery and the right ventricle. There are no absolute clinical methods of diagnosis in relatively mild cases. The clinical changes relating to the heart may be few. It is often extremely difficult to differentiate other symptoms and signs which are caused by an underlying disease of the pulmonary parenchyma. The roentgenological demonstration of the enlargement of the pulmonary artery and its conus has been described in detail by Parkinson (15). He recommends that roentgenograms be taken in the lateral, oblique and anteroposterior positions. In the anteroposterior position the conus is difficult to make out, the left pulmonary artery is often obscured and at times the right pulmonary artery can be visualized. The conus is best seen, he believes, in the right anterior oblique position. Enlargement of the right ventricle is often impossible to make out in the anteroposterior position. At times enlargement of the right side of the heart is demonstrated in the left anterior oblique position. We believe that these findings are often equivocal.

In some cases of *cor pulmonale,* electrocardiograms show right axis deviation. However, if complicating factors (such as systemic hypertension, aortic valvular disease and coronary sclerosis) cause left ventricular hypertrophy, no axis deviation or even left axis deviation may be observed. If the size of the heart decreases and if rotation of its axis occurs as the result of chronic changes in the lungs and mediastinum, axis deviation by electrocardiogram becomes unreliable. Probably the

only true objective measurement of the right ventricle is being used by Robb *et al.* (16) who clearly established its width by the rapid injection of 70 per cent radiopaque diodrast, with roentgenograms taken at correct intervals of time. This method is excellent but its use is obviously limited because the technique is difficult, the procedure is involved and coöperation of a skilled team is necessary. By tomography Petrilli (17) has been able to demonstrate the pulmonary arteries during the early stages of dilatation caused by pulmonary hypertension. Tomography in our opinion should receive much more attention because of its simplicity and general adaptability. The methods described, with the possible exception of Robb's diodrast and Petrilli's tomography, do not necessarily establish a definite diagnosis of chronic *cor pulmonale.*

The diagnosis of early right-sided heart failure is extremely difficult to establish. The earliest objective signs of this failure are elevation of venous pressure and prolongation of the circulation time from arm to lung. Venous pressure may rise further in the presence of abdominal pressure due to congestion of the liver. Differential circulation times (arm to lung and arm to tongue) with ether and decholin or with other suitable drugs are of distinct value in the diagnosis of early right-sided heart failure. According to Oppenheimer and Hitzig (19) some degree of failure is always indicated if the arm to lung time is prolonged; and if, with this prolongation, the lung to tongue time is normal, then pure right-sided heart failure is present.

When frank failure of the right side of the heart uncomplicated by left-sided failure and pulmonary congestion occurs, diagnosis is relatively easy. Abnormalities of rhythm were not seen in any of our cases of primary right-sided heart failure. The treatment, consisting of the same measures used in other forms of heart failure, is, however, most difficult. Digitalization, oxygen therapy and venous section usually are of only transient benefit. That the prognosis is poor was emphasized by Scott *et al.* (13) who reported deaths during first failure in 84 per cent of a series of 43 cases. Despite therapy, dyspnoea and cyanosis are progressive, distension of the cervical veins and oedema increase and the patient gradually sinks into coma and death. On the other hand, death may occur suddenly.

As Harrison (18) and Scott *et al.* (13) have emphasized, in pure right-sided heart failure paroxysmal nocturnal dyspnoea and Cheyne-Stokes breathing rarely occur because there is no pulmonary congestion. In

left-sided failure with secondary right-sided failure, marked congestion and rigidity of the alveoli develop which are believed to cause dyspnoea by reflex action through the vagus (18).

Pathology: If the patient dies in whom chronic *cor pulmonale* either with or without failure was suspected, what are the pathological criteria for diagnosis? The pathological alterations are reflected in changes in the lungs, in the pulmonary artery and its branches and in the right side of the heart. Absolute diagnosis depends above all on the presence of definite hypertrophy which is often accompanied by dilatation in the outflow tract (the outflow tract of the right ventricle extends from the apex to the pulmonary orifice; the rest of the ventricle is considered as the inflow tract). Changes in the other components measured may be present, but unless definite hypertrophy of the right ventricle can be demonstrated by suitable pathological methods, we cannot make a diagnosis. The right ventricle should measure at least 5 mm. in width; sometimes it is as wide or wider than the left ventricle. In hypertrophy on the right side, the weight of the heart is usually not great and may be normal (between 250 and 500 g.). (See following table.)

	WEIGHT OF HEART IN GRAMS							
	200–250	250–300	300–350	350–400	400–450	450–675	Not weighed	Total
Number of cases with failure.....	1	4	4	2	2	3	5	21
Number of cases without failure..	1	2	3	3	1	4	6	20
Total.....	2	6	7	5	3	7	11	41

	WIDTH OF RIGHT VENTRICLE IN CENTIMETRES					
	0.5	0.6	0.7	0.8	0.9	Total
Number of cases with failure.....	9	6	5		1	21
Number of cases without failure..	5	8	6	1		20
Total.....	14	14	11	1	1	41

Neither changes in the inflow tract of the right ventricle, the liver or the spleen nor oedema are encountered.

Since pathological diagnosis of chronic *cor pulmonale* depends upon the observation of cardiac hypertrophy on the right side, the heart should

be examined by a specific method, such as that recommended by Herrmann and Wilson (20). A brief description of their method follows:

> The auricles as well as the mitral and tricuspid leaflets are removed. The aorta and pulmonary artery are separated from the ventricular muscle. The fixed ventricles are divided by cuts at right angles to the long axis of the heart in a series of sections, each about 1.5 cm. in thickness. A clear-cut line running through the septum can now be seen. The ventricles are divided into right and left by following this line. Near the anterior and posterior surfaces of the heart where the line forks, the cut bisects the angle between the forks. The septal muscle is not considered. The ventricles are weighed separately and the ratio between right and left is determined (20).

In our cases, conclusions were drawn from postmortem reports, and the method described unfortunately could not be used. If the right ventricular wall measures 5 mm. in width, definite hypertrophy is present. If the right ventricle is markedly dilated, then the width of the right ventricular wall might conceivably be less and hypertrophy still be present. Therefore, if any error exists in our series, it is one of understatement rather than overstatement. Certainly, if in any case the diagnosis of hypertrophy of the right side of the heart is in doubt, the Herrmann and Wilson method of sectioning should be used. In 15 cases of *cor pulmonale* secondary to tuberculosis, the left ventricular wall measured between 15 and 20 mm. in diameter. Griggs *et al.* (10) indicated that a left ventricular wall measuring 15 mm. or more is hypertrophied. In these 15 cases there was no evidence clinically or from pathological examination of preëxisting hypertension.

Griggs *et al.* (10) noted unexplained left-sided hypertrophy in conjunction with hypertrophy on the right side in some of their cases. Kountz *et al.* (22) found hypertrophy of the left ventricle in 10 cases of emphysema in which the right ventricle was also hypertrophied. Two causes of this left-sided hypertrophy have been given, namely anoxaemia, and continuity of the spirally arranged musculature of the heart (23). The cause of left ventricular hypertrophy in hearts in which one would expect only pure hypertrophy on the right is, however, in our opinion still unexplained.

Alterations in the lung on gross and microscopical examination may suggest an aetiology of chronic *cor pulmonale*. There may be evidence of pulmonary hypertension due to the alterations which may be reflected in the changes in the pulmonary artery and its radicals. The pulmonary arteries may show periarterial fibrosis and atherosclerosis, and the small

arteries may show subintimal fibrosis, atrophy of media and increase of elastica in the intima and adventitia. Parker *et al.* (21) stated that malignant changes in the vessels of the lung occur following mitral stenosis, but not in other conditions. They based their conclusions on examination of 12 cases of pulmonary emphysema, one of marked kyphosis with sclerosis and 19 of chronic interstitial pneumonitis. In one of our cases changes of the vessels occurred which we interpreted to be of a malignant or hyperplastic character (see case 1). The pulmonary conus may be dilated and measure over 8 cm. in circumference and the leaflets of the pulmonary valve may be opaque.

In failure, evidence of back pressure with involvement of the inflow tract on the right side of the heart, including dilatation of the right auricle, is accompanied by congestion of the abdominal viscera and often by marked oedema. When the cause of the oedema is uncertain, studies of serum protein and congo-red tests are indicated. It is the accepted belief that if the liver and the spleen are congested, they are also enlarged. In tuberculosis, however, patients have had the disease for a long period of time and their organs have tended to become smaller than normal. In most autopsies, the heart is removed first and the blood is drained; consequently the weight of both the liver and the spleen decreases further. Therefore, enlargement of liver and spleen is a poor criterion for the diagnosis of congestion. Grossly, the evidence of congestion is the typical nutmeg appearance, while microscopically the central areas are distended with blood. Occasionally the congestion may be marked enough to cause destruction of the parenchyma of the liver and the appearance of polymorphonuclear cells. In none of our cases was the condition so advanced or prolonged that so-called cardiac cirrhosis had developed.

Association with tuberculosis: Lesions of the lungs associated with tuberculosis which have been thought to cause some degree of occlusion of the pulmonary arterial tree are:

1: Obliterative pleuritis
2: Productive lesion with secondary emphysema
3: Collapse therapy
    a. Pneumothorax with thickened pleura
    b. Thoracoplasty
4: Silicosis
    a. Interstitial fibrosis
    b. Emphysema
    c. Bronchial artery and pulmonary artery communication
5: Chronic miliary tuberculosis

We investigated the incidence of chronic *cor pulmonale* in 330 cases of pulmonary tuberculosis from autopsies recorded between 1933 and 1940 at the San Francisco City and County Hospital. Patients under the age of sixteen and those who had minimal tuberculosis and died on the general medical wards were not included. The duration of illness in the entire group of 330 patients was extremely difficult to ascertain from the histories, and therefore we have omitted the figures. In the group were 53 cases of chronic *cor pulmonale*, or an incidence of 16 per cent. Forty-nine patients were males who died at an average age of fifty years and 4 patients were females who died at an average age of forty-one years. Of the remaining 277 cases, 235 patients were males who died at an average age of forty-nine years and 42 patients were females who died at an average of thirty-three years. In 67 cases the causes of death were exudative lesions with the pneumonic type of tuberculosis. Thirty-two patients had miliary disease, 21 patients died of nontuberculous conditions and 33 patients had tuberculosis of organs other than the lungs. The remaining 124 patients had mixed productive and exudative lesions. None of the patients in whom *cor pulmonale* did not occur had silicosis although 26 of them had minimal emphysema. These observations agree with those made by Hirsch (as previously stated) according to which chronic *cor pulmonale* does not have time to develop in rapidly progressing tuberculosis of the pneumonic type.

In the study of the cases with chronic *cor pulmonale*, other causes of hypertrophy of the right side of the heart, such as left ventricular failure, coronary disease and even beri-beri heart, were discarded. In 12 out of the 53 cases, definite failure was found together with intrinsic cardiac disease of the endocardium or myocardium; they were therefore eliminated. A heart which is well compensated will decompensate if a further burden is thrown upon it, especially if its reserve is low. Therefore, occult coronary disease may be brought out by pulmonary hypertension resulting from extensive pulmonary disease. This condition is analogous to a perfectly compensated heart with a masked myocardial weakness pushed into failure by hyperthyroidism. The one patient in this group with a beri-beri heart had a history and physical findings of vitamin insufficiency, and the pathological changes were compatible with such a diagnosis, notably enlargement with dilatation, subendocardial vacuolation, oedema and interstitial fibrosis. In the absence of coronary disease, subendocardial vacuolation may be observed in a fair percentage of cases of pulmonary tuberculosis in which after death a small rather

than a large heart is found. Thiamin chloride determinations should be done on the urine of patients suspected of having chronic *cor pulmonale*. What rôle vitamin B_1 deficiency plays in the development of right-sided heart failure will require further investigation.

In our opinion, pleural thickening plays a very small rôle in the development of *cor pulmonale*. As can be seen from the control cases in this study, 90 patients had complete obliteration of both sides with no evidence of hypertrophy of the right side of the heart. In the 277 cases, obliteration of pleural cavities occurred as follows:

In 90 it was complete on both sides;
In 90 it was partial on both sides;
In 72 it was partial on one side and complete on the other side;
In 5 it was complete on one side and absent on the other side;
In 14 it was partial on one side and absent on the other side;
In 6 it was absent on both sides.

We believe that pleural thickening plays an important part in producing obstruction of the pulmonary blood flow only when it is particularly marked, extensive and chronic, as in empyema. Of the 53 cases of chronic *cor pulmonale* examined, complete bilateral obliteration of the pleural cavity was observed in 33, partial obliteration of the pleural spaces in 17 and free pleural spaces on both sides in 3.

In the group of 41 cases of *cor pulmonale* finally studied, no lesions could be demonstrated, either grossly or microscopically, in the pericardium, the myocardium or the endocarium. They were divided into two groups, the first consisting of 21 cases with failure and the second of 20 cases without failure. The 21 cases with failure were again divided into two groups: the first, those in which failure was minimal, usually terminal, and was of little significance clinically; and the second, those in which heart failure on the right side dominated the picture and was a major cause of death. It should be noted here that oedema is not always an evidence of right-sided heart failure. In our control group of 277 cases, oedema was observed in 23. In 7 cases the cause of oedema was amyloid, in 4 it was caused by nutritional defects, in 7 it was due to miscellaneous causes and in 5 its cause was undetermined. Of the 21 cases of *cor pulmonale* with heart failure, profound failure on the right side was observed in only 2 (see case 2). Of the remaining 19 cases, marked anthracosilicosis was found in 4, in one a productive miliary lesion was found and in the remaining 14 chronic productive lesions of

long duration with secondary emphysema and obliteration of the plerual spaces were observed. In the 26 cases with emphysema discovered in the 277 controls, it was always of minimal extent and short duration. In the 14 cases of chronic *cor pulmonale*, emphysema was chronic and extensive. These factors were extremely difficult to evaluate but it is our impression that emphysema is an important factor in the production of chonic *cor pulmonale*.

As to collapse therapy, in pneumothorax there are certain obvious structural alterations. We know that compression of the pulmonary artery or its radicals will produce *cor pulmonale*, and in collapse therapy this might be brought about. In 31 cases of pneumothorax studied at autopsy at the Rutland State Sanatorium in Massachusetts (24), the average weight of the heart was only 287 g., but the average width of the right ventricular wall was 0.5 cm. In 20 out of the 31 cases, the right ventricles measured 5 mm. or more: in 11 cases, 5 mm.; in 8 cases, 6 mm.; and in one case, 7 mm. In 16 cases empyema was observed. In 11 of the 16 cases the right ventricles measured 5 mm. or more; in 6 cases, 5 mm.; in 4 cases, 6 mm.; and in one case, 7 mm. The three largest hearts in the series, which were found in cases of empyema, weighed 540, 430 and 420 g. respectively, and the right ventricular wall in each case measured 6 mm. in width. In these 3 cases the collapse was marked, of long duration, the pulmonary artery showed moderate atherosclerotic changes, the pleura was thickened because of empyema and there was extensive fibrosis throughout the lungs in the areas of disease. It can be seen that a slightly higher incidence of hypertophy of the right side of the heart occurred in the group with empyema which also showed the largest hearts. The duration of the empyema and the degree of collapse were difficult to determine from the clinical histories and the pathological findings. It was our impression, however, that the greater the compression by empyema and the longer its duration, the more apt was chronic *cor pulmonale* to develop. Whether bronchial and pulmonary arterial communication exist in this pathological condition is unknown. Gardner (25) found hypertrophy of the right side of the heart in 3 out of 15 cases of pneumothorax. He did not give the measurements of the right side of the heart and did not state the duration of collapse or whether empyema was present. In the series studied at the San Francisco City and County Hospital, the number of cases of pneumothorax which came to autopsy was too small and the information given too meagre to draw any conclusions.

Thoracoplasty also is sometimes a cause of hypertrophy of the right side of the heart. When a patient dies soon after this operation, the time interval is too short for the changes to develop in the right side of the heart. We had 2 patients both of whom were found at autopsy to have chronic *cor pulmonale*, and in each case the time interval between operation and death was long. (See case 3.) We wish to emphasize that chronic *cor pulmonale* should be considered before collapse therapy is begun. If it is already present without failure or with slight failure, then it is conceivable that frank failure might result if compression of the pulmonary arterial tree is increased.

It has been shown that in silicosis right-sided failure and hypertrophy of the heart are common. Cole *et al.* (26) have demonstrated the presence of marked fibrosis in the interstitial tissue, especially in the acute cases. They described these changes minutely beginning with congestion of the vessels, the laying down of collagen with interruption of vascular pathways, and finally the complete interruption of oxygen exchange between the alveoli and their capillaries. This interstitial fibrosis produces marked anoxaemia. Wood (27) has devised a method by which in various types of pulmonary disease communication between the bronchial artery and the branches of the pulmonary artery may be shown by injecting a radiopaque substance into the bronchial artery. That these communications have been especially prominent in cases of silicosis, indicates the need for collateral circulation due to the obstruction of the pulmonary flow. These communications also exist in tuberculosis but to what degree and in what significance we are unable to state. Certainly, further studies of injection of the bronchial artery in cases of chronic *cor pulmonale* are indicated. Wood (27) has postulated that because of the marked difference in pressures in the bronchial and pulmonary arteries (120 and 30 mm. Hg, respectively) some increase of the pressure of the pulmonary artery may ensue. In silicosis, emphysema is also prominent but secondary to large areas of fibrosis which have replaced the pulmonary parenchyma. When tuberculosis is complicated by silicosis or anthracosilicosis, death occurs earlier than in uncomplicated silicosis. If, however, tuberculosis is superimposed, death occurs more rapidly because of the infection. But the important point is that in this group (anthracosilicosis plus tuberculosis) heart failure on the right side is much more common than in tuberculosis alone (28). Four of our cases of chronic *cor pulmonale* in which slight failure occurred were complicated by anthracosilicosis.

Chronic miliary tuberculosis is a diffuse process which involves the interstitial tissue, and at times causes fibrosis, obstructs blood flow, interferes with oxygen exchange and rarely causes pulmonary hypertension with secondary hypertrophy of the right side of the heart (see case 4). Usually the duration of miliary disease is too short for hypertrophy to develop and the pathology is often exudative rather than productive so that dilatation alone results. This extensive interstitial reaction is somewhat comparable to the findings in acute silicosis (26).

In our 20 cases without failure, the factors were the same as those in the cases with failure.

CASE REPORTS

Case 1: This patient, a thirty-one year old Swiss painter, entered the hospital on July 11, 1939. He had been in good health until November, 1936, at which time he caught a cold. A cough developed which gradually became productive, and the sputum contained streaked blood on rare occasions. Two and one-half years before admission he began to note dyspnoea on exertion which was progressive. He had orthopnoea and oedema of the ankles during the week before admission. During the three previous years he had lost 16 pounds. He was ambulatory up to the day of admission. Physical examination showed a markedly cyanotic, dyspnoeic male. Neither Cheyne-Stokes breathing nor paroxysmal dyspnoea was observed. Râles were present throughout both lungs. The cardiac sounds were rapid and forceful; the rhythm of the heart was regular. There was a markedly accentuated P_2; the pulse rate was 120. Blood pressure was 100/80. The patient had no clubbing of the nails. The liver was three finger breadths below the costal margin. There was pitting oedema of both ankles. Haemoglobin was 130 per cent; the red blood count was 6.7 million; sedimentation rate was 16 mm. Although the patient was given digitalis and put into an oxygen tent, no change was noted in his condition and he died on July 12, 1939.

Autopsy: Anatomical diagnoses: Bilateral noncaseating tuberculosis with foci in myocardium, kidney, liver and lymph nodes (? Boeck's sarcoid); chronic *cor pulmonale*; congestion of liver and spleen; dependent oedema.

The positive findings, grossly, were as follows: The body was that of a markedly cyanotic male. The vessels and lungs were greatly distended. Each lung weighed 950 g. Extensive, fine fibrosis was spread throughout the lungs, being most marked at hilar regions and apices. Both pleural spaces were obliterated. A moderate degree of pulmonary atherosclerosis was seen. No cavitation or caseation was noted. The heart weighed 450 g., and the right auricle and ventricle were markedly dilated and hypertrophied. The right ventricular wall measured 8 mm. The bundles of muscle were plump. The

coronary vessels were normal. The tricuspid valve was dilated, measuring 15 cm. The leaflets of the pulmonary valve were opaque and had a circumference of 8 cm. The left ventricular wall measured 1.5 cm. The liver weighed 3,000 g. and was congested. The spleen weighed 350 g. and was congested. There was some oedema of the ankles.

Microscopically, in the lungs a wide-spread noncaseating process with many foci with epithelioid cells and giant cells was observed. Pulmonary atherosclerosis was marked. Some vessels, especially arterioles, gave evidence of hyperplastic changes suggesting profound pulmonary hypertension. This was the only case in which these changes occurred. There was no evidence of silicosis or fungus disease. Liver and spleen showed considerable congestion.

Comment: This is a classical case of chronic *cor pulmonale* with marked failure. Unfortunately this patient was in the hospital less than twenty-four hours and a thorough study could not be made. Certainly he had extensive tuberculosis of the noncaseating variety. This type of tuberculosis is not exceedingly rare, is often chronic, and patients who have this type of disease may die of definite right cardiac failure. This patient also had pathological evidence of hypertension of the pulmonary circuit, as reflected by the hyperplastic changes in the pulmonary arterioles.

Case 2: Patient, a thirty year old male, entered the hospital on August 29, 1939, and died on January 16, 1940. His chief complaints on entrance were substernal pain of one year's duration, a productive cough, loss of weight of 30 pounds, marked fatigue and dyspnoea. Physical examination revealed an undernourished though fairly well developed man. Râles were present throughout both lung fields. The liver was palpable one finger breadth below the costal margin. Blood pressure was 110/68. The heart was not enlarged. Its rhythm was regular and P_2 was greater than A_2. No oedema was present. Haemoglobin was 90 per cent, red blood count 6.41 million, white blood count 15,000, polymorphonuclear cells 87 per cent, sedimentation rate 32 mm. On January 11, 1940 the urine contained an occasional granular cast and a trace of albumin. Previous examinations had been negative. Roentgenograms showed bilateral diffuse infiltration and a cavity at the apex of the right lung. The sputum was positive for tubercle bacilli. Electrocardiogram showed no axis deviation. Venous pressure was 30 cm. of water, but differential circulation times were not determined. The clinical course was characterized by increasing dyspnoea and cough with an occasional rise in temperature. On November 2, 1939 the patient had sudden extreme dyspnoea and pain on the left side of the neck, with marked bilateral subcutaneous emphysema of the upper chest, of the neck and of the face. Roentgenograms showed no evidence of pneumothorax. This condition cleared, reappeared within the next two

weeks, but disappeared completely in one month. There was no Cheyne-Stokes breathing or paroxysmal dyspnoea. The patient gradually became more dyspnoeic and orthopnoeic and somewhat suddenly died January 16, 1940.

Autopsy: Anatomical diagnoses: Bilateral chronic pulmonary tuberculosis with cavitation, acinous and acinous-nodose tuberculosis, chronic *cor pulmonale*, congestion of liver and spleen.

On gross examination the body was well developed and well nourished. There was no oedema of the extremities and no clubbing of the fingernails or toenails. Both pleural cavities were completely obliterated by fibrous adhesions. The heart weighed 375 g. The left ventricle measured 1.2 cm., the right 0.7 cm. The right auricle was moderately dilated. The coronary vessels were normal. The circumference of the valves was as follows: tricuspid 12.5, pulmonary 7, mitral 10 and aortic 7 cm. The right lung weighed 1,125 g. and the left 675 g. Both lungs were markedly involved with densely packed productive lesions projecting above the cut surface because of increase in connective tissue. There was an old cavity measuring 4 by 3 cm. in the right lower lobe, and a similar one at the base of the right upper lobe. No cavities were seen in the left lung. The pulmonary artieries showed rare patches of atherosclerosis. The liver weighed 1,265 g. and showed a nutmeg appearance. The spleen weighed 210 g. and was deeply congested.

Microscopical examination: The lungs showed a productive type of tuberculosis but little tendency to caseation, with compensatory emphysema between the areas of infiltration. There was also some tuberculous involvement of the bronchi with destruction of their wall. The interlobar and interlobular fissures showed an increase of connective tissue, and the pleura was greatly thickened. The liver showed extensive congestion of the central areas with even some slight necrosis of liver cells and the presence of a few polymorphonuclear cells. The spleen also showed congestion.

Comment: The changes in the lung were due entirely to an extensive, productive tuberculosis. The mediastinal emphysema which had developed in this case was probably due to escape of air along the interstitial tissue secondary to tuberculosis of the bronchi, and may have contributed in a slight degree to the production of right-sided heart failure. This was a classical case in which chronic *cor pulmonale* with marked failure was a major cause of death.

Case 3: M. H., a forty-two year old female, was found to have unilateral tuberculosis with a small cavity at the apex of the left lung five months following a streptococcus septicaemia in 1933. Within the next two years she had symptoms which suggested laryngeal and intestinal tuberculosis. She continued to work as a nurse until 1935. The previous year, she had had an unsatis-

factory pneumothorax over a period of only five months. She was admitted to the hospital in November, 1935 at which time a one-stage, five-rib thoracoplasty was done. She did poorly because of the development of an infection in her operative incision. She recovered within six months and was again able to do part-time work. Although she had some dyspnoea, her serious symptoms did not occur until two weeks before her last entry on November 20, 1939, which was four years after the thoracoplasty. At that time she began having episodes of severe paroxysmal dyspnoea and coughing. She would bring up about one ounce of foamy, pink sputum and within one or two hours would feel better. These attacks occurred while she was resting in bed as well as while she was up and around. Opiates, atropin and oxygen gave slight relief. Her venous pressure during an attack was 35 to 38 cm., but between attacks it was normal. During the attacks numerous moist râles were heard throughout the lungs; between attacks there were few râles and some bronchial wheezes. Tests of the circulation times could not be done because the patient was too ill. The dyspnoeic spells occurred with increasing frequency, severity and cyanosis. She grew progressively worse and on February 4, 1940 expired. The respirations ceased before the pulse. There was no oedema.

Laboratory findings: The urine showed a very faint trace of albumin, with 20 to 100 clumps of white blood cells. Haemoglobin was 102 per cent, red blood count 5.10 million, white blood count 9,100, polymorphonuclear cells 80 per cent, lymphocytes 14 per cent, sedimentation rate 22 mm. Vital capacity was 575 cc. Electrocardiogram showed deviation of the right axis and evidences of myocardial damage. Roentgenograms of the chest showed a cavity at the apex of the left lung with extensive fibrosis throughout, and minimal disease of the right apex.

Autopsy: Anatomical diagnoses: Chronic pulmonary tuberculosis, thoracoplasty on the left with cavitation in left upper lobe, marked fibrosis of the left lung, emphysema of the right lung, chronic *cor pulmonale*, congestion of liver and spleen.

The positive findings were, grossly, as follows: The body was that of an emaciated female weighing about 85 pounds with evidence of considerable loss of weight. No clubbing of the fingernails was present. The chest was much smaller on the left than on the right, and there was a scar of an old thoracoplasty situated posteriorly on the left. There was no oedema. The left pleural cavity was completely obliterated, and there were a few adhesions at the right apex. The right upper and middle lobes of the lungs were emphysematous. There was a slight amount of honeycombing at the right apex which represented areas of fibrosis. Fine reticular fibrosis was definite throughout this lung. The right lung weighed 360 g., and the left 515 g. The left lung was shrunken, noncrepitant, and had a thickened fibrous pleura. There was an open cavity in the left upper lobe which measured 3 cm. in diameter.

The bronchus opening into it was narrowed and slightly ulcerated. The interlobar fissure was fused, and the lower lobe was a mass of fibrous tissue, prominent bronchi, and encapsulated areas of caseation. The heart weighed 225 g. The right ventricle was definitely hypertrophied and dilated, especially in its outflow tract. The left ventricle showed no hypertrophy. The coronary vessels were normal. The right ventricular wall measured 0.7 to 0.4 cm., and the left, 1.1 cm. The circumference of the tricuspid valve was 12 cm. and that of the pulmonary valve 7 cm. The liver weighed 1,165 g. and the spleen 110 g. Both were definitely congested. The other abdominal organs showed some atrophy.

Microscopical examination: The right lung showed emphysema and some fibrosis of the interalveolar septa, with a few scattered old tubercles. The left lung showed productive tuberculosis with pronounced fibrosis about vessels and bronchi obliterating the architecture. Fibrosis was also present in the interstitial tissue. The bronchus leading to the open cavity was serially sectioned and showed definite tuberculosis with destruction of muscle and absorption of cartilage. The myocardium on the right side was not remarkable. Liver and spleen showed congestion. No other areas of tuberculosis were observed.

Comment: In spite of the fact that this patient had an apparently excellent thoracoplasty, chronic *cor pulmonale* developed and was an important cause of death. It must be emphasized that the cavity for which the thoracoplasty was done had remained open and that there was also quite marked tuberculosis of the bronchi of this lung. The inflammation about these bronchi caused some periarterial fibrosis, and it is interesting to speculate how much this had to do with her pulmonary hypertension. One must raise the question whether in other patients who have apparently good thoracoplasties chronic *cor pulmonale* with a poor prognosis may not develop. This would have been an excellent case for injection of the bronchial artery.

Case 4: The patient, a twenty-seven year old Filipino mess boy, entered the hospital on May 20, 1935. His illness had begun only three days previously in the form of haemoptysis. He had lost 3 pounds in weight during the three months before hospitalization. Physical examination revealed that his chest was apparently normal, his fingernails were slightly clubbed, but he had no oedema. Roentgenograms taken May 22, 1935 showed active tuberculosis in the upper lobe of the right lung. At the time of entry his temperature was 104° to 101°F.; it persisted on this level until his death. On July 2, 1935 a fluoroscopic examination showed acute dissemination; a roentgenogram taken

on July 19, 1935 confirmed this observation. The patient became more dyspnoeic and toxaemic and expired on July 25, 1935.

Autopsy: Anatomical diagnoses: Miliary tuberculosis of lungs, liver, spleen, lymph nodes and bone marrow; chronic pulmonary tuberculosis of right upper lobe; congestion of lungs and liver.

On gross examination the body was markedly emaciated. No oedema was noted. Bilaterally a few fibrous adhesions were seen at both apices. There were 400 cc. of clear fiuid in the left pleural cavity. The heart weighed 320 g. The right auricle and ventricle were slightly dilated and the right ventricle measured 0.5 cm. Each lung weighed 1,100 g. Scattered throughout the lungs there were numerous miliary tubercles which had peripheral gray borders and stood up above the cut surface suggesting an increase in the connective tissue. There was an old cavity at the apex of the right lung 4 cm. in length. Tubercles could be visualized in the spleen and liver. Microscopically the tubercles in the lung were of a rather productive character and showed but little tendency to caseation. Between them were zones of compensatory emphysema. There were tubercles of a similar nature in the liver, spleen, lymph nodes and bone marrow. The liver and spleen were moderately congested.

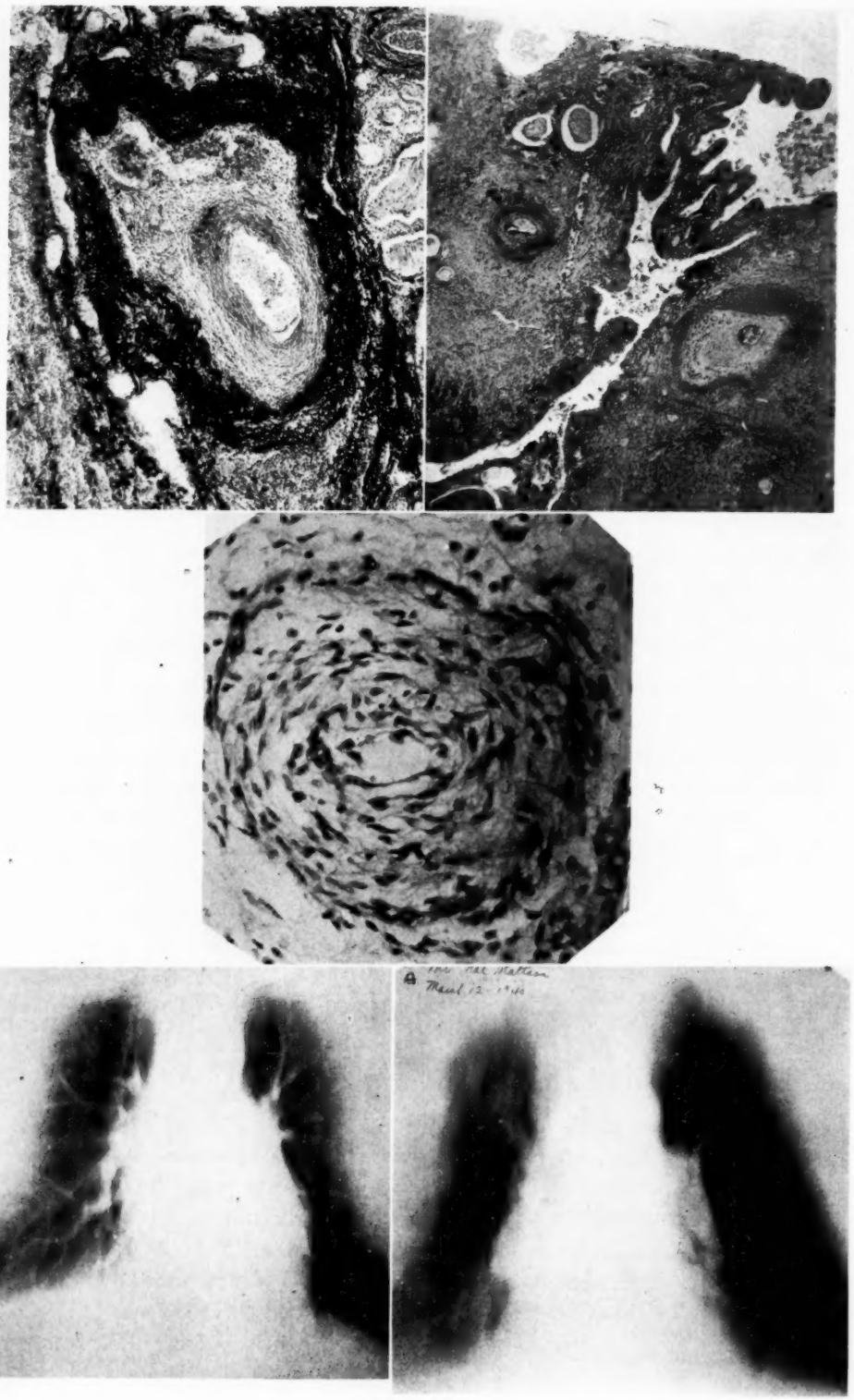
Comment: Although in this case miliary tuberculosis had a clinical course of about four weeks, the lesions produced in the lung were productive rather than exudative, and because of their extensiveness they produced chronic *cor pulmonale* which was partially responsible for the death of the patient. Chronic *cor pulmonale* in miliary tuberculosis is rare, and the 32 other cases of miliary tuberculosis in the control group did not show this picture.

CONCLUSIONS

1. The incidence of hypertrophy of the right side of the heart with marked failure is low in uncomplicated pulmonary tuberculosis.

2. Right-sided hypertrophy without failure occurs in about 6 per cent of all patients who die of pulmonary tuberculosis. (This varies with the type of patient.)

3. In several types of cases hypertrophy of the right side of the heart with or without failure tends to develop. These include cases of chronic productive tuberculosis of long duration with secondary emphysema (common), chronic productive miliary tuberculosis (rare) and pulmonary lesions complicated by silicosis or anthracosilicosis. Pneumothorax of long duration with marked collapse and thickened pleura at times causes hypertrophy of the right side of the heart. Thoracoplasty may cause this hypertrophy. The existence of chronic *cor pulmonale* should be



FIGS. 1–5

considered before any type of collapse therapy is instituted. Pleural adhesions are not important in the pathogenesis of *cor pulmonale.*

4. If cardiac and pulmonary disease are combined, causing pulmonary hypertension, right-sided heart failure will appear early.

5. The changes in the pulmonary arterial tree are usually degenerative and only rarely hyperplastic.

6. The cause of occasional hypertrophy of the left side of the heart in association with disease of the lung which should cause only right-sided hypertrophy remains unexplained.

7. The clinical and pathological criteria necessary for the diagnosis of chronic *cor pulmonale* have been discussed.

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Fig. 1. (Top left.) Pulmonary artery (× 20) Weigert-Van Gieson stain. Subintimal fibrosis with atrophy of media with marked increase in elastica.

Fig. 2. (Top right.) Atherosclerosis of small branches of the pulmonary artery. (20)

Fig. 3. (Center.) Hyperplastic endarteritis of branch of pulmonary artery. (× 333)

Fig. 4. (Bottom left.) Tomograph (Petrilli) normal pulmonary arteries.

Fig. 5. (Bottom right.) Tomograph (Petrilli) abnormal pulmonary arteries.

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TREATMENT OF TUBERCULOSIS AND DIABETES[1, 2]

A Ten-Year Experience

RICHARD M. McKEAN, GEORGE C. THOSTESON AND NATHAN BROOKS

In the past ten years, 15,361 patients with pulmonary tuberculosis have been admitted to Herman Kiefer Hospital. Of these, 1.59 per cent had associated diabetes mellitus. The number in this special group admitted each year has increased from 7 in 1929 to 40 in 1939. Most reports on this subject have painted a rather disheartening picture for this group of patients. In 1934, Myers and McKean (1) presented to the National Tuberculosis Association a report of the first 80 cases suitable for analysis, covering the first five years of this service. The current review concerns 117 patients from the second five years (1934–1939), with the special purpose to determine whether or not, by comparison, any significant changes in the management and results in this group of patients have occurred.

SYMPTOMS AND PHYSICAL FINDINGS

There have been no essential changes in these respects. An overwhelming majority of patients presented cavitation, sputum containing tubercle bacilli, glycosuria, hyperglycaemia and a known history of diabetes mellitus. On admission most of the patients were underweight, and in many the diabetes was uncontrolled.

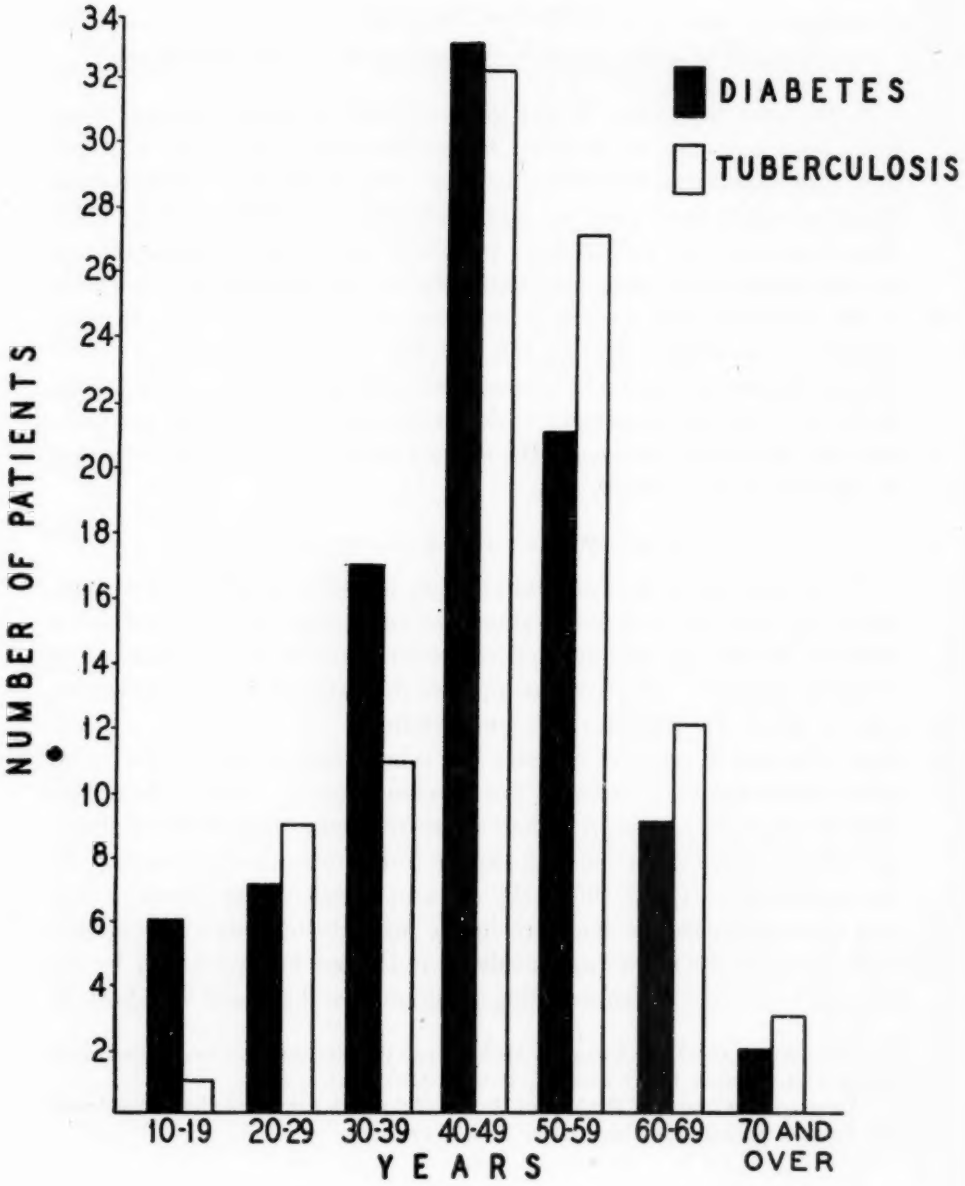
Age: The ages of onset of diabetes and tuberculosis in the current series differ somewhat from those of the previous report. Table 1 indicates that the majority of this group had a history of onset of both the diabetes and the tuberculosis in the fifth decade (forty to forty-nine years). In the earlier series (1929–1934), the diabetes began in the fourth decade and the tuberculosis in the sixth in the majority of instances. A possible factor in the earlier age incidence in the second series may be the intensive tuberculosis case-finding program that has been in effect in

[1] From Wayne University College of Medicine and the Metabolic Division of the Tuberculosis Unit, Herman Kiefer Hospital, Detroit, Michigan.

[2] Presented at a session of the Medical Section of the 35th annual meeting of the American Trudeau Society, Cleveland, Ohio, June 3, 1940.

TABLE I

AGE OF ONSET



Detroit in the past few years. Analyzing this point further (table 2), it is noted that in 47.6 per cent of the cases, the development of the diabetes preceded that of the tuberculosis. In this group, the onset of the diabetes occurred under forty years of age in 56 per cent. In the group in which the history (and discovery) of each disease was simultaneous, 87 per cent had the onset of the diabetes over the age of forty. Here again, it is possible that the tuberculosis case-finding program was reponsible for bringing these patients to the attention of their physicians with the result that, not only the tuberculous disease was detected, but also an otherwise unsuspected diabetes was discovered. In only 7 per cent did the development of the tuberculosis definitely antedate the diabetes. In this group the tuberculosis was detected after the age of forty in most cases. It is possible that the presence of the infectious process in these cases had much to do with precipitating the diabetic process.

TABLE 2

Age of onset—105 patients

ONSET DIABETES UNDER 40	DIABETES PRECEDES TUBERCULOSIS	ONSET DIABETES OVER 40	ONSET DIABETES UNDER 40	ONSET SAME	ONSET DIABETES OVER 40	ONSET TUBERCULOSIS UNDER 40	TUBERCULOSIS PRECEDES DIABETES	ONSET TUBERCULOSIS OVER 40
28	50	22	6	48	42	1	7	6
56%	47.6%	44%	12.5%	45.7%	87.5%	14.2%	6.7%	85.8%

Classification of the tuberculosis: The two groups (1929–1934 and 1934–1939) parallel each other closely in respect to the type of tuberculous lesion. In the current series, 74 per cent of the cases had far advanced disease, 19 per cent moderately advanced and 4 per cent minimal; 1.8 per cent had pleural effusion and one case (0.9 per cent) had miliary involvement.

TREATMENT OF TUBERCULOSIS

For some time the thoracic surgeon had been reluctant to consider the patient with coexistent diabetes mellitus and tuberculosis for collapse therapy. This attitude has changed (table 3), and the patients, having this combination of diseases, are given whatever form of collapse treatment is indicated by the tuberculous process. The presence of the diabetes does not materially influence the choice of the procedure. Pneumothorax and phrenic nerve surgery are employed readily. If more

extensive procedures, such as pneumonolysis and thoracoplasty seem advisable, the metabolic service is consulted as to the degree of control of the diabetes, and the operation is done when the patient is deemed in best possible control under the circumstances.

Eighty-one per cent of the patients in the second series received some form of collapse therapy compared with 68 per cent in the previous group. This is indicative of more liberal consideration by the thoracic surgeons, since the distribution of the tuberculous disease is essentially the same in both groups. Nine patients received thoracoplasty and are part of 11 cases reported elsewhere by Thosteson and McKean (2). It is appropriate to mention here that in this group of thoracoplasties, there were no immediate postoperative deaths. Two of 3 deaths resulted ultimately from the tuberculous disease, the first, four and one-half months and the second, two years after the last stage. The third death was due to coronary heart disease.

TREATMENT OF THE DIABETES MELLITUS

The diabetic management in this type of patients is essentially the same as in an uncomplicated case, namely, the control of the glycosuria and hyperglycaemia. On admission, a weighed diet is prescribed according to the nutritional state of the patient and the severity of the diabetes. The patient is made to regain his normal weight and is maintained at that level. Obese patients who are 20 per cent or more over standard normal weight are reduced slowly to the standard level. There is no evidence in this study to indicate that this slow weight reduction has been deleterious to the patients as regards the tuberculous process. The diabetes in this type of patient becomes relatively easy to control by diet alone as a rule, a point favoring this procedure.

Unless the patient on admission is very ill or the diabetes appears to be especially severe (marked hyperglycaemia or ketosis) diet alone is used to render the urine free of sugar. The usual initial formula is protein 75 g., fat 100 g. and carbohydrate 100 g. If this procedure is not successful in a reasonable period of time (seven to ten days), insulin is started. In either case, after this initial period of observation, diet changes are made to meet the nutritional requirements and insulin modified to bring about urinary and blood sugar control.

In the first five-year group, unmodified or regular insulin (being the only type available) was used exclusively, but in the current series, the modified insulins, such as protamine zinc and solution zinc insulin crys-

tals (crystalline insulin) have been used in a steadily increasing proportion, singly or in combination. The value of the modified insulins has been demonstrated in many reports, and our experience in general corroborates this evidence. However, it is our opinion that these newer forms of insulin have not influenced the actual course of either disease differently from regular insulin, excepting inasmuch as they have minimized the number of injections required for control and thus simplified the diabetic management.

TABLE 3

Treatment of tuberculosis

	1929–34		1934–39	
	Number	Per cent	Number	Per cent
Total patients	80		117	
Collapse therapy used	54	67.5	95	81.2
No collapse therapy	26	32.5	22	18.8
Pneumothorax:				
Unilateral	22	27.5	45	38.4
Bilateral	2	2.5	4	3.4
Phrenic:				
Crushing	10	12.5	34	29.1
Phrenicectomy			4	3.4
Phrenic and pneumothorax	17	21.3	14	11.9
Pneumonolysis	1	1.3	8	6.8
Thoracoplasty:				
1 stage	2	2.6	2	1.7
2 stages			3	2.5
3 stages			2	1.7
Bronchoscopy:				
Negative			10	8.5
Ulcers			1	0.8
Pneumoperitoneum			2	1.7

Whenever possible, P.Z.I.[3] alone has been used in these patients. It has been necessary to supplement this preparation with either regular or crystalline insulin in 35 per cent of instances where it has been used. If, by reason of frequent insulin reactions or other factors, P.Z.I. appeared to be impractical, crystalline insulin was administered two or three times daily rather than regular insulin. The crystalline insulin

[3] Protamine zinc insulin.

is reputedly a purer product, and appears to cause fewer hypoglycaemic reactions than regular insulin in large multiple doses. Eighty-two per cent of the 1934–39 series required insulin. This is essentially the same as in the earlier group. This percentage is materially higher than that obtained in another clinic in Detroit handling nontuberculous patients where 43 per cent required insulin. Such evidence supports the belief that in general the presence of tuberculosis (like any other infection) tends to render the diabetic status more severe.

Although 5 patients gave a history of coma prior to admission, none developed this complication during their hospitalization. Two deaths were thought to be due to profound hypoglycaemia. Frequently, prior to death it is necessary to reduce the insulin dose rapidly, due to insufficient glucose intake, deficient stores of hepatic glycogen or possibly to an inadequate assimilation of the ingested glucose. It is sometimes difficult to maintain control during this period of rapid change.

In comparing the dietetic prescriptions used in this study with those of the previous period, distinct differences were noted (table 8). In the first period the average diet was protein 62 g., fat 162 g., carbohydrate 108 g., a total of 2,138 calories. The current series averaged protein 69 g., fat 135 g., carbohydrate 143 g., total calories, 2,121. This represents an increase of 7 g. in the protein, not a material difference. The ratio of protein to weight is essentially the same, 1.17 g. per kilogram. The greater differences noted are an increase in the carbohydrate of 35 g. and a reduction of the fat of 19 g. This variation has been practically isocaloric, resulting in no material difference in the total calories. This tendency to provide a higher carbohydrate allowance conforms with the trend throughout the country. It is of interest that even with the increased carbohydrate allowance, the average dose of insulin remains 42 units, identical with that of the earlier study.

The diets are prepared in the metabolism unit supervised by the dietitian. Such an arrangement permits the diets to be carefully controlled and modified as necessary to meet appetite variations and complications, such as haemoptysis and enteritis. The available glucose of the prescription is distributed equally in the three meals, except when P.Z.I. is used, and in these instances a night feeding of 10 to 20 g. of available glucose is given. This amount is usually subtracted from the breakfast allowance. The night feeding offsets early morning hypoglycaemia, and by reduction of the glucose given at breakfast lessens mid-day hyperglycaemia.

COMPLICATIONS

Table 4 shows the complications encountered in the 117 patients of the second five-year series. Pleural effusion predominates in the tuberculous group. Nineteen varieties of nontuberculous complications were found, and 7 surgical procedures not related to the tuberculous process were done, as indicated. Since pleural effusion is the most frequent complication, table 5 is presented to show the effect of this com-

TABLE 4

Complications

TUBERCULOUS	NONTUBERCULOUS	
	Medical	Surgical
1. Pleural effusion.....23	1. Heart.....4	1. Cataract.....1
2. Empyema, tuberculous 8	2. Nephritis.....2	2. Enucleation.....1
Empyema, mixed..... 1	3. Nephrolithiasis.....1	3. Thyroidectomy.....2
3. Fistula, broncho-pleural..... 2	4. Syphilis.....4	4. Hernia.....1
4. Haemoptysis..... 6	5. Coma prior admission.5	5. Leg amputation.....1
5. Spontaneous pneumothorax..... 5	6. Cataract.....2	6. Finger amputation.....1
6. Enteritis..... 8	7. Glaucoma.....1	7. Nephrolithotomy.....1
7. Laryngitis..... 6	8. Retinitis.....3	
8. Genito-urinary tuberculosis..... 2	9. Asthma.....1	
9. Spondylitis..... 1	10. Thyrotoxicosis.....2	
10. Osteitis (finger)..... 1	11. Thyroid adenoma.....1	
11. Pleuritis, obliterative.. 1	12. Severe reaction.....2	
12. Miliary disease..... 1	13. Hypertension.....2	
13. Meningitis..... 1	14. General arteriosclerosis 3	
14. Peritonitis, obstructive 1	15. Hemiplegia.....1	
Peritonitis, without obstruction..... 1	16. Ventral hernia.....1	
15. Bronchial ulcers..... 2	17. Inguinal hernia.....4	
16. Skin tuberculosis..... 1	18. Fracture, non-union...1	
	19. Gangrene, feet.....2	
	20. Cholecystitis.....1	

plication on a patient whose diabetes was controlled. Whenever there is an unaccountable loss of glucose tolerance in these patients, one can suspect some impending disturbance such as fluid, empyema or spread of the tuberculous disease. This loss of tolerance frequently manifests itself by increasing glycosuria before the actual causative factor can be demonstrated. Close observation of the diabetic status is imperative. Our routine is to obtain a weekly blood sugar, taken in the fasting state one week, at 10 a.m. the second week, at 2 p.m. the third week and fast-

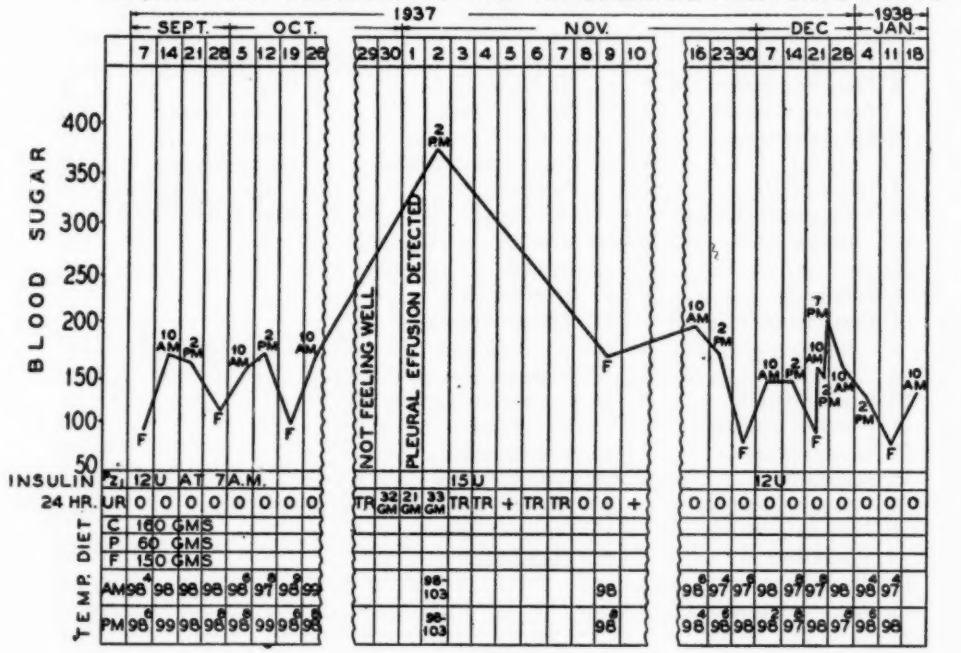
ing the fourth week. The twenty-four-hour urine is collected in four fractions, from breakfast to lunch, lunch to supper, supper to bedtime and bedtime to breakfast. This information facilitates ready adjustments of insulin dosage or diet depending on the degree and distribution of glycosuria reported. When all fractions are negative, a single twenty-four-hour specimen is examined. When the patient has undergone surgery or when the tolerance has otherwise been acutely disturbed, immediate reports are requested. In addition to the metabolism dieti-

TABLE V

EFFECT OF ACUTE EPISODE (EFFUSION) ON DIABETES

DIABETES 2 YRS

L.G., AGE 45, M. PULMONARY TB - III B INTRAPLEURAL PNEUMONOLYSIS 7-1-37



tian, a resident physician particularly interested in diabetes is on duty to make prompt adjustments. The close surveillance of the diabetic status in this combination of diseases cannot be too strongly emphasized.

RESULTS

In an effort to determine factors in each disease which may influence death, the results are correlated in table 6. It will be noted that of 42 cases dying in the hospital, 76 per cent (32 patients) had moderately severe or severe diabetes compared with 56 per cent of the groups dis-

charged improved or unimproved. Also, of the group dying in the hospital, 90 per cent had far advanced tuberculosis compared with 66 per cent of the cases discharged living. Thus, while both the severity of the diabetes and the extent of the tuberculous lesion seem to be the major factors in death, it would appear that, on the basis of the figures presented above, the extent of the tuberculous lesion is by far the more potent factor, providing, of course, that the diabetes is adequately treated.

TABLE 6

Relationship of condition at discharge to type of disease and severity of diabetes

	IMPROVED—29			UNIMPROVED—12			DEAD—42		
DIABETES→	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Tuberculosis ↓ Pleural Effusion			2	1					
I Exudative	1								
I Productive	1	1				1			
II Exudative	1							1	1
II Dense exudative	1							1	
II Productive			1		1				1
II Mixed		1	2						
III Exudative	1						4	4	3
III Dense exudative	1	1	1	2	2	2	3	5	4
III Productive	4	1	2		1	2	2		4
III Mixed	5	1	1				1	4	4
Total	15	5 9 (14)		3	4 5 (9)		10	15 17 (32)	

It is generally assumed that the prognosis in patients with associated diabetes mellitus and pulmonary tuberculosis is more grave than in those wherein tuberculosis is not associated with diabetes. We were concerned with attempting, in this respect, to make some tenable comparison. Because of the multiplicity of factors involved in each of these chronic diseases, it is statistically unreliable to arrive at a single fatality rate. For instance, patients dying within a month after admission of prostrating far advanced tuberculosis are not statistically comparable to patients entering with moderately advanced disease and expiring after twenty-four months. Inasmuch as the majority (74 per cent) of

our patients had far advanced tuberculosis, it seems fair to compare them with a similar group having far advanced tuberculosis not associated with diabetes mellitus. Ninety-three per cent of our far advanced cases were classed as III B, and 7 per cent as III C. Table 7 represents

TABLE 7

Comparison of mortality

SIX MONTH PERIOD	PERCENTAGE PATIENTS DYING IN PRECEDING AND CURRENT PERIOD	
	Tuberculosis *and* diabetes	Tuberculosis *without* diabetes
1st	25	30
2nd	43	47
3rd	55	54
4th	57	58
5th	57	60
6th	60	63
7th	60	65
8th	64	66
9th	68	68
10th	75	69

TABLE 8

Summary

	1929–1934	1934–1939
Patients reported	80	117
Age of onset (majority)		
Diabetes	30–39 years	40–49 years
Tuberculosis	50–59 years	40–49 years
Average hospital stay	10.9 months	10 months
Classification of tuberculosis		
Far advanced	63 (78.8%)	80 (74.3%)
Moderately advanced	14 (17.5%)	21 (19.4%)
Minimal	3 (3.8%)	4 (3.7%)
Received collapse therapy	54 (67.5%)	95 (81.2%)
Received no collapse therapy	26 (32.5%)	22 (18.8%)
Diet*		
Average protein	62 g.	69 g.
Average carbohydrate	108 g.	143 g.
Average fat	162 g.	134 g.
Average calories	2138 calories	2121 calories
Insulin*		
Number requiring average dose	27 (84.4%), 42 units	76 (82.6%), 42 units
Died in hospital	37.1%	35.9%

* Figures on Diet and Insulin based on patients whose Diabetes was observed in the Hospital for more than 6 months: 1929–34, 32 patients; 1934–39, 92 patients.

a comparison or mortality, in six-month periods, of 81 cases having associated tuberculosis and diabetes with 241 cases of tuberculosis unassociated with diabetes, each group presenting 93 per cent classed as III B and 7 per cent as III C.[4] The figures obtained parallel each other closely. It would thus appear that the presence of a controlled diabetes does not alter the outlook in an individual with pulmonary tuberculosis.

SUMMARY

The distribution of cases in respect to the type of tuberculous disease and average severity of the diabetes remains about the same over a period of ten years (table 8).

A marked increase in the use of collapse therapy in general has occurred.

From the metabolic standpoint, an increase in the carbohydrate allowance and a reduction of fat in the diets has been most outstanding. These differences have offset each other so there has been no appreciable change in the total calories.

Slightly more than 80 per cent of the patients required insulin with an average dose of 42 units. This remains the same for each period despite the increase in the carbohydrate portion of the diet in the second period. Protamine zinc insulin is used whenever feasible.

The mortality of cases with associated diabetes mellitus and tuberculosis parallels closely that of pulmonary tuberculosis alone. The outstanding factor in the fatal case appears to be far advanced tuberculous disease rather than the severity of the accompanying diabetes mellitus, providing the latter has been adequately controlled. However, the greater difficulty in maintaining normal blood sugar levels and aglycosuria in some cases probably plays a subsidiary rôle.

Acknowledgment of our indebtedness is made to Dr. Bruce H. Douglas, Controller of Tuberculosis, Detroit Department of Health; to the Superintendent of Herman Kiefer Hospital, Mr. George Phillips, and to the medical, surgical and dietetic staffs of the Tuberculosis Unit for their splendid coöperation.

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PRIMARY TUBERCULOSIS IN ADOLESCENTS AND YOUNG ADULTS[1]

HAROLD L. ISRAEL AND ESMOND R. LONG

In recent years, during which the rate of primary tuberculous infection in childhood has dropped, the character and prognosis of first infection tuberculosis in adolescents and young adults have become problems of increased interest. With the continuing use of the large number of sanatorium and hospital beds for tuberculosis now available, and the isolation that may be expected of an increasingly large proportion of the total tuberculous population, it is to be expected that tuberculous infections in childhood will become still less common in future years. An increasingly large number of persons, if infected at all, will be infected for the first time in adolescence or adult life. To this group may be added those who have been infected one or more times before, but so slightly and so infrequently that the sensitiveness to the tubercle bacillus conferred by the first or subsequent infections has disappeared. Such cases should be included for discussion in any consideration of primary tuberculosis in post-childhood years.

Present views on the pathological character and seriousness of first infection tuberculosis in adolescence are widely divergent. A recent review (1) gives the opposing claims in some detail. In brief summary, the opinions that have been expressed may be listed as follows: (*1*) Primary tuberculosis in adolescence is like that commonly observed in childhood both in pathological character and in benign clinical course. (*2*) Primary tuberculosis in adolescence is anatomically like that commonly observed in childhood, but is more serious in its clinical course. (*3*) Primary tuberculosis in adolescence is anatomically different from that observed in childhood, resembling reinfection type tuberculosis as it is seen typically in adults, but clinically follows the benign, nonprogressive course characteristic of first infections in childhood. (*4*) Primary tuberculosis in adolescence is different from that commonly observed in children both in its anatomical character and in its clinical

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia, Pennsylvania.

course, anatomically resembling the reinfection type in adults, and having in addition a tendency to follow a progressive, unfavorable course.

The divergence of opinion is well illustrated by two recent reports. One concludes that the primary lesion in the young adult is so benign that "for the individual it is better if he never knows that this transient pulmonary lesion existed" (2). The other reports that "primary infection in adult age gave rise in 19 cases out of 47, to pulmonary tuberculosis which often proved to be progressive and malignant" (3).

Before the merits of the several claims are considered, it will be well to review the views generally accepted on the character of primary tuberculosis in children and reinfection type tuberculosis in adults. In *Diagnostic Standards* published by the National Tuberculosis Association in 1935 the "childhood type" of tuberculosis was described as follows: A parenchymal lesion usually occurs, which is localized in a lower lobe or lower part of an upper lobe, often with involvement of the associated bronchopulmonary or tracheobronchial lymph nodes; caseous lesions usually become calcified and encapsulated by fibrous tissue, but occasionally such lesions progress to excavation; areas of infiltration commonly resolve, leaving trivial scars or none at all.

In the same edition of *Diagnostic Standards* the "reinfection type tuberculosis" characteristic of adults was pictured as follows: The adult type of tuberculosis usually occurs in adults, but may occur in children, and is the result of continued infection (exogenous or endogenous); localization is usually in the upper third of the lung; at the time of the first clinical manifestations the subapical region is usually involved; regional lymph nodes usually are not grossly involved; caseous lesions are usually followed by excavation or fibrosis or both; calcification is a very slow process; areas of infiltration may recede with the production of more or less fibrous tissue.

In the "tentative edition" of *Diagnostic Standards* published in 1938 what are essentially the same types of tuberculosis are designated "primary tuberculosis" and "reinfection tuberculosis", rather than childhood and adult type tuberculosis, but the descriptions of the lesions concerned and their clinical course are not greatly changed. Encapsulation and calcification are recognized as the prevalent types of regression, and spread by lymphatic and haematogenous dissemination or continuity as the prevalent type of progression in the primary type. In the reinfection type, resorption and fibrosis are recognized as the prevalent manner of retrogression, and caseation, liquefaction, excavation and bronchogenic spread as the prevalent type of progression.

In the latest edition of *Diagnostic Standards* (1940) the designations are again changed by the committee charged with revision of this text to the "primary phase" and the "reinfection phase" of tuberculosis. The descriptions of the lesions concerned are not significantly different from those presented in previous editions. The definition of the primary phase should be noted, namely, "that phase of the morbid processes which follows directly and uninterruptedly the first implantation of tubercle bacilli." The word "uninterruptedly" is very important, for the distinction between primary disease and reinfection disease of haematogenous onset depends on the interpretation of this word. The committee was evidently well aware of the difficulties involved and added, after the definition of the primary phase, "It is obvious that in many instances no sharp line of demarcation can be drawn between primary and reinfection tuberculosis," and, in a later paragraph, "it is not always possible on clinical and roentgenological evidence to differentiate primary and reinfection phases of tuberculosis."

Presumably tuberculosis can be considered primary if there is reliable evidence that shortly before the appearance of the lesion, tuberculous infection was not present. The only practical means by which this evidence can be secured is the tuberculin test. Unless a patient is known to have been negative to tuberculin shortly before observation of a tuberculous lesion, the latter cannot with certainty be considered primary, regardless of its anatomical character.[2] Considerable difference of opinion exists, however, as to that point in time beyond which the influence of reinfection must be assumed. As Scheel (4) has written, he considers lesions proceeding to a fatal issue eighteen months after first infection as primary, while, as he says, similar instances are cited as examples of the effect of reinfection by Myers. A third viewpoint is represented by Burrell (5) who believed that the term primary should be restricted to disease appearing within the few weeks of the preallergic period. In the discussion that follows, the patients who are cited as examples of primary tuberculosis had negative intracutaneous reaction to 1.0 mg. of Old Tuberculin or 0.005 mg. of Purified Protein Derivative Tuberculin, and negative X-ray examination of the chest, four to fourteen months before detection of the pulmonary lesion. The smaller the

[2] That the anatomical character of "primary" tuberculosis is not uniform in adults is shown by the recently reported painstaking studies of Terplan. Instances are recorded of typical Ghon complexes as well as nonapical pulmonary foci without regional lymph node enlargement. On the other hand, Terplan found typical Ghon complexes which were apparently the result of reinfection, for older primary lesions were demonstrable. (Terplan, K.: Anatomical studies on human tuberculosis, Am. Rev. Tuberc., 1940, *42*, supplement.)

interval, presumably the greater is the probability that the lesion was due directly to the primary infection. Special and separate consideration will be given to those cases in which the tuberculin test was negative shortly before the tuberculous lesion had appeared, but on one or more previous occasions had been positive.

Taking into consideration the several views recently expressed on the character and course of first infection tuberculosis in adolescents, and the definitions commonly accepted for the anatomical character of first infection tuberculosis in children and reinfection type tuberculosis in adults, and following the criteria just expressed for considering observed tuberculosis as primary, we have tried to determine if first infection tuberculosis in adolescents and young adults follows any pattern relating it to primary tuberculosis in children or the reinfection type tuberculosis common in adults.

The following varieties of anatomical form and clinical tuberculosis taken by primary tuberculosis have been observed in our experience in adolescents and young adults. The item "pleurisy with effusion" is included, for experience from all quarters has shown that primary pulmonary tuberculosis in adolescents may first be manifested, not by pulmonary infiltration, but by minimal involvement of the lung parenchyma or hilum lymph nodes, and more or less massive pleural effusion.

OBSERVED TYPES OF PRIMARY TUBERCULOSIS IN ADOLESCENTS AND YOUNG ADULTS

I. Anatomically like primary tuberculosis in childhood.
   A. With favorable clinical course
      1. Asymptomatic
         a. With tendency to calcify
         b. Without tendency to calcify
      2. Symptomatic
   B. With unfavorable clinical course
      1. Rapidly progressive
         a. Progressive pulmonary infiltration
         b. Miliary tuberculosis

II. Anatomically like reinfection type tuberculosis in adults.
   A. With favorable clinical course
      1. Asymptomatic
   B. With unfavorable cinical course
      1. Slowly progressive

III. Pleurisy with effusion.

Examples of these types of primary tuberculosis have been observed either in the chest clinic of the Henry Phipps Institute or in auxiliary enterprises, such as investigation of the development of tuberculosis in nursing students and the study of tuberculosis among Indians. In some categories several examples have been observed, and in some but one or two. The following case histories illustrate the types observed.

I. A 1a: Anatomically like primary type tuberculosis in childhood, with favorable clinical course, asymptomatic, with tendency to calcification of the lesions.

H. C., male, white, Jewish, born in 1913, was tuberculin-negative in April, 1924, October, 1926 and January, 1928. In December, 1928, when the patient was fifteen years old, he gave a two-plus reaction to 0.01 mg. of Old Tuberculin. X-ray examination of the chest in April, 1924 and April, 1927 showed no abnormalities. In December, 1928, when the tuberculin reaction was positive, X-ray examination showed pulmonary infiltration with slight but definite hilum lymph node enlargement (figure 1). In September, 1929 calcification was observed at the site of the pulmonary infiltration and in the lymph node. X-ray films in February, 1935 and March, 1940 (figure 2) showed no significant change from the appearance in September, 1929. No symptoms were associated with the development of the lesion.

I. A 1b: Anatomically like primary type tuberculosis in childhood, with favorable clinical course, asymptomatic, without tendency to calicification.

R. M., female, Negro, born in 1914, was tuberculin-negative in 1924, 1925, 1926 and December, 1927. In February, 1929, when the patient was fifteen years old, she gave a three-plus reaction to 0.01 mg. of Old Tuberculin. X-ray film of the chest in 1926 showed no abnormalities, but a film made in February, 1929, at the time a positive tuberculin reaction was first observed, showed a

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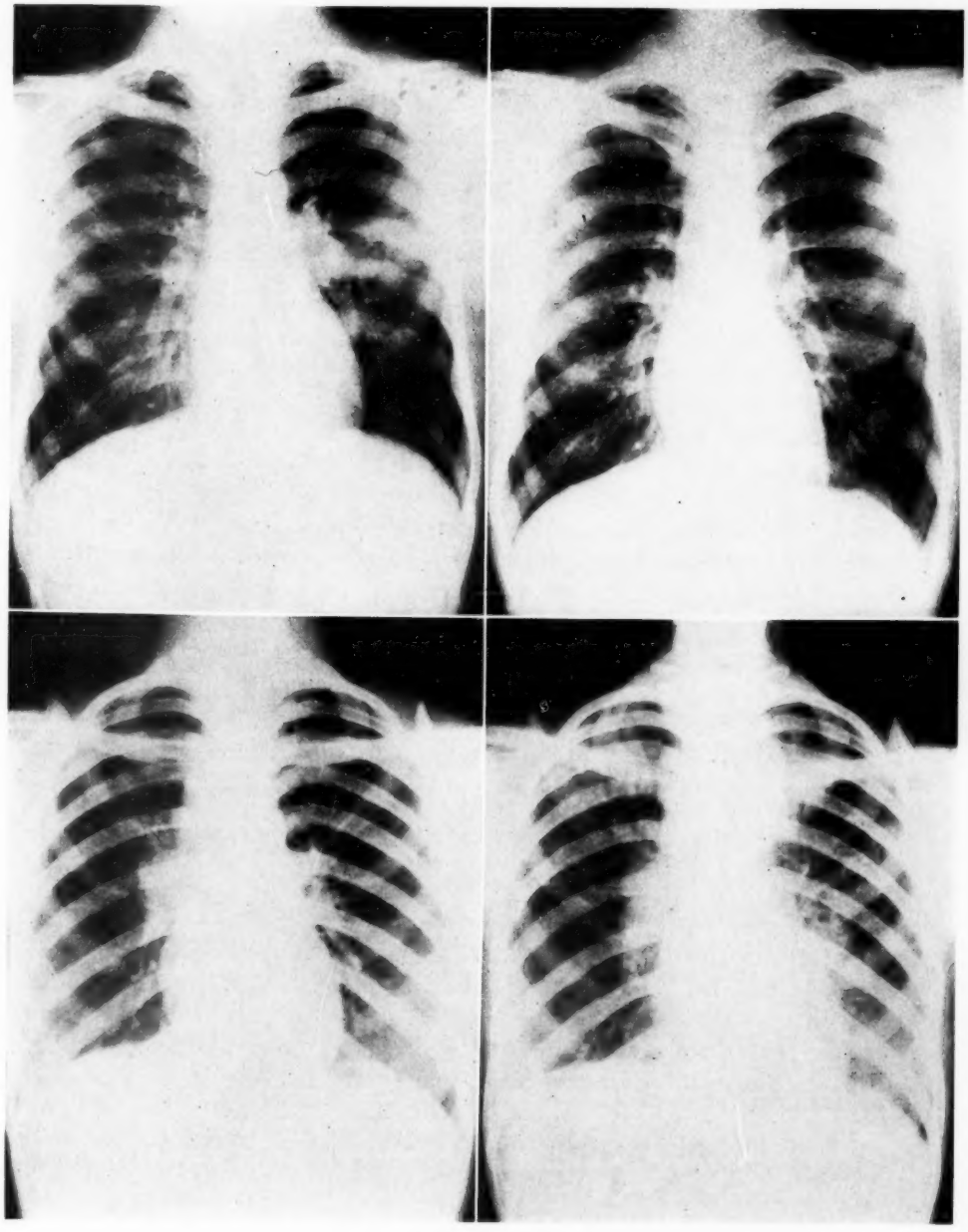
FIG. 1. upper left H. C., male, white, age fifteen. Film of December 4, 1928. There is infiltration in the middle third of the left lung, with slight but definite lymph node enlargement at the hilum.

FIG. 2. upper right H. C., film of March 16, 1940. There is a density representing calcification, within the hilum shadow at the posterior seventh rib. The presence of a peripheral nodule is not definite.

FIG. 3. lower left M. C., female, Negro, age fourteen. Film of January 26, 1939. There is massive lymph node enlargement at the right hilum and within the mediastinal shadow. There is scanty infiltration in the posterolateral third interspace on the right side, and within the circle of the first rib on the left side.

FIG. 4. lower right M. C., film of March 23, 1939. There is extensive bilateral infiltration and cavitation. The lymph node enlargement is increased.



FIGS. 1–4

dense infiltration in the upper right lung with enlargement of the tracheobronchial lymph nodes. Regression of the lesion followed. In July, 1932 a few light spots remained at the level of the right clavicle. In a film made in November, 1939 the lungs and mediastinum appeared normal. At the time of examination in February, 1929, when the lesion was discovered, there were no symptoms of illness. The patient reported that she had had an attack of grippe during the preceding months, but it was of short duration.

I. A 2: Anatomically like primary type tuberculosis in childhood, with favorable clinical course, but with symptoms.

B. T., male, Negro, born in 1922, was negative to tuberculin in November, 1929. He gave a very slight reaction in November, 1938 (one-plus to 0.005 mg. of Purified Protein Derivative Tuberculin) and a strong reaction in July, 1939 when he was seventeen years old (three-plus to 0.000,02 mg. of Purified Protein Derivative Tuberculin). No abnormalities were found on X-ray examination in November, 1938, but in March, 1939 X-ray examination showed a probable infiltration below the right clavicle and massive lymph node enlargement at the right hilum. An X-ray film made in October, 1939 showed no change. Symptoms were present at the time of the first X-ray film showing a lesion, that is, in March, 1939. During this month he had developed fever, headache and dizziness. He entered the Philadelphia General Hospital in April, 1939 after a loss of 20 pounds in weight. Subsequently the fever declined and the lost weight was regained. The patient was free from symptoms in January, 1940.

I. B 1a: Anatomically like primary type tuberculosis in childhood, with unfavorable clinical course, rapidly progressive, with progressive pulmonary infiltration.

M. C., female, Negro, born in 1924, was negative to tuberculin in September, 1938. In January, 1939, when the patient was fifteen years old, she gave a three-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. X-ray film of the chest in September, 1938 showed no abnormalities, but in January, 1939 small areas of infiltration were apparent in each pulmonary apex and there was great enlargement of the hilum lymph nodes (figure 3). A film in March, 1939 (figure 4) showed marked progression of the pulmonary infiltration with bilateral cavitation. Severe toxaemic and respiratory symptoms coincided with the apparent onset and continued. The girl entered the Philadelphia General Hospital in February, 1939 and died in June, 1939.

I. B 1b: Anatomically like primary type tuberculosis in childhood, with unfavorable clinical course, rapidly progressive, with the develop-

ment of miliary tuberculosis. The only case encountered which might fit into this category does not satisfy the necesssary criteria, but is suggestive.

M. W., female, Indian, born in 1919, was negative to tuberculin in May, 1936. In May, 1937 when she was eighteen years old, the patient developed a pleural effusion with an appearance in the X-ray film suggesting disseminated pulmonary lesions. In June, 1937 there was definite pulmonary infiltration with widely disseminated involvement. The patient died of miliary tuberculosis in September, 1937.

II. A 1: Anatomically like reinfection type tuberculosis in adults, with favorable clinical course, without symptoms.

G. C., female, white, born in 1919, a nurse in training, was tuberculin-negative in February, 1937 and October, 1937. In February, 1938, when she was nineteen years old, she gave a three-plus reaction to 0.005 mg. of Purified Protein Derivative Tuberculin. Chest X-ray films in February, 1937 and February, 1938 failed to show any abnormalities. A film in August, 1938, however, disclosed a scanty pulmonary infiltration above the right clavicle, with no apparent involvement of the tracheobronchial lymph nodes. A film in December, 1938 showed regression of the lesion, and another in June, 1939 showed apparent complete scarring. There were no symptoms at any time.

II. B 1: Anatomically like reinfection type tuberculosis in adults' with unfavorable clinical course, slowly progressive.

C. D., female, white, born in 1919, a nurse in training, was tuberculin-negative in February, 1938 and June, 1938. In October, 1938, when she was nineteen years old, she gave a three-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. Chest X-ray film examination was negative in February, 1938, but apparently positive in August, 1938, when what appeared to be a light infiltration was found in the middle third of the left lung. In films made in October, 1938 moderately dense infiltration was found in the left lung extending from the clavicle to the 9th rib posteriorly, with a small cavity below the clavicle. A film made in February, 1939 showed apparent improvement, with closure of the cavity and some clearing of the infiltration, but a film in July, 1939 showed fresh disease in the right lung. The patient had been in good health until October, 1938, when she developed chest pain, which was especially severe on breathing. She was at rest in bed from October, 1938 to July, 1939. Although the lesion was spreading, she appeared in good health. No further progression occurred during the following year, but in

June, 1940, the lesion as seen in the X-ray film was still flocculent and considered dangerous.

III. Pleurisy with effusion.

R. D., female, white, born in 1919, a nurse in training when first examined, was tuberculin-negative in September, 1937, February, 1938 and June, 1938. In October, 1938, when she was nineteen years old, she gave a three-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. Chest X-ray examination was negative in September, 1937, September, 1938 and November, 1938. In January, 1939, however, three months after the first observation of a positive tuberculin reaction, X-ray film examination showed a massive pleural effusion in the left hemithorax. In September, 1939 examination showed thickening of the pleura. Symptoms coincided with the apparent onset, in January, 1939. The patient had chest pain, severe on breathing. She was at rest in bed from January to September, 1939, when she resumed her studies.

As noted previously, in a discussion of primary tuberculosis in adolescents, those cases should be considered in which lesions appear in persons recently negative to the tuberculin test but previously known to be positive or presumed once to have been positive because of the presence of a calcified lesion of the type accepted as tuberculous in origin. Three examples will be given with lesions corresponding to the three main divisions in the preceding classification, that is, (*1*) resembling primary infection in childhood, (*2*) resembling reinfection type tuberculosis in adults and (*3*) characterized by pleural effusion.

I: Development of a lesion anatomically like primary type tuberculosis in childhood, in a patient recently negative to tuberculin, but presumed once positive because of the presence of a calcified pulmonary lesion.

E. A., female, Indian, born in 1923, was negative to tuberculin in January, 1936 and March, 1937. In March, 1938, when she was fifteen years old, she gave a three-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. X-ray examinations in April, 1936 and January, 1937 showed a calcified nodule in the left lung but no other lesion.[3] In January, 1938, X-ray examination showed the development of an infiltration in the middle third of

[3] Recent studies by Dr. J. D. Aronson and Dr. Robert M. Saylor on the Indian reservation from which this patient came, have suggested that some calcified nodules in the lungs may possibly be the residues of arrested coccidioidmycosis. There was no special reason to suspect previous coccidioidal disease in this patient.

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the right lung, with enlargement of the hilum lymph nodes. A film made in June, 1938 showed no change from the picture in January, 1938. In June, 1939, however, X-ray examination showed retrogression both of the infiltration and the lymph node enlargement. There was no impairment of health until early in 1940, when respiratory symptoms developed. X-ray examination made on March 6, 1940 showed consolidation at the right apex and extensive infiltration in the upper left lung. The disease was progressive and the patient died of tuberculosis in September, 1940.

II: Development of a lesion anatomically like reinfection type tuberculosis in adults in a patient recently negative to tuberculin, but presumed once positive because of the presence of a calcified pulmonary lesion.

J. C., female, white, born in 1915, a nurse in training at the time of examination, was tuberculin-negative in September and December, 1935 and March, 1936. In June, 1936, when she was twenty-one years old, she gave a three-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. X-ray examinations in September, 1935 and April, 1936 showed no abnormalities except a calcified nodule and node in the right hemithorax. In October, 1936 in the first X-ray examination after the tuberculin reaction had become positive, scanty infiltration was found below the left clavicle. In films made in October, 1937 and October, 1938 this was seen to fluctuate slightly in extent and density. A film made in February, 1939 showed an increase in density of the infiltration. In January, 1940 a cavity had developed below the level of the left clavicle. The patient had had an illness diagnosed as grippe in April, 1936, but was free from symptoms between then and November, 1939, when she suffered from fatigue and slight cough and began to lose weight.

III: Development of pleurisy with effusion in a patient recently negative to tuberculin, but previously positive.

C. G., female, white, born in 1922, was positive to tuberculin (two-plus to 1.0 mg. Old Tuberculin) when first examined in August, 1928. She was negative to tuberculin in August, 1929, July, 1933, March, 1936 and January, 1937. In June, 1937, when she was fifteen years old, she gave a two-plus reaction to 0.000,02 mg. of Purified Protein Derivative Tuberculin. X-ray film examinations in August, 1928 and March, 1936 showed no abnormalities. In June, 1937, at the time the tuberculin reaction was first observed to be positive after being negative for nine years, X-ray examination showed scanty tuberculous infiltration in the right lower lung. Five months later, in November, 1937, a massive pleural effusion developed in the right pleural cavity. This was gradually absorbed and in January, 1940 films showed only pleural thickening

in the right hemithorax. This patient had had no known contact with tuberculosis until a brother developed the disease in 1936. The infection observed in 1937 was probably from this source. She had few symptoms at the time of the pleural effusion. She rested six months in bed and after the absorption of the fluid, appeared entirely well.

DISCUSSION

An impressive feature of this study has been the paucity of instances of authenticated primary tuberculosis in adolescents under our observation. Although the change of tuberculin reaction from negative to positive has been observed in many hundreds of young adults in our experience, development of pulmonary lesions within the ensuing year has been infrequent. The majority of adolescents who have developed tuberculosis under our observation have had an interval of much more than a year between infection and development of the lesion, and it would be unjustifiable to assume such lesions are due to the primary infection.

With few exceptions, patients cited in the foregoing case histories developed lesions within a year of a record of a negative tuberculin test. The lesions of these adolescents may be considered as probably the result of first infection. The examples cited show a wide variation in both roentgenological type and clinical behavior, in contrast to the stereotyped response of childhood. Racial factors appear to play a rôle in the heterogeneity of the manifestations. Lesions resembling the primary tuberculosis characteristic of childhood, that is, with pulmonary infiltration and hilar or mediastinal lymph node enlargement, proved more common among Negroes than whites; in the single instance (H.C.) of an anatomically typical lesion in a white youth, the lymph node enlargement was minimal.

The difference between Negro and white youths in the frequency of adenopathy cannot be due to a greater incidence of primary infection among Negro adolescents. Studies (6, 7) have shown that the proportion of Negroes reaching adolescence in the tuberculin-negative state is smaller than among whites.

The difference between white and Negro patients in respect to adenopathy, as is well known, is not limited to primary tuberculosis. Many observers have emphasized the frequency of caseous tuberculosis of the hilum lymph nodes in the ordinary pulmonary tuberculosis of the Negro. The racial difference was illustrated recently in the results of a study (8) of patients diagnosed within a five-year period at the Henry Phipps

Institute as having pulmonary tuberculosis. Among 345 adult Negroes, 7 had disease with prominent hilar or mediastinal adenopathy, while no instance of this was observed among 245 adult white patients.

It is noteworthy that only one instance of acute miliary tuberculosis in a recently infected youth was found. Although acute miliary disease has been reported, especially by Scandinavian investigators (3, 9), to be a not uncommon result of primary infection in adults, no instance of this occurred in our dispensary experience, or in our observations of medical and nursing students.

Considerable evidence is accumulating that loss of tuberculin sensitivity is frequent. Whether this is accompanied by complete loss of altered response to tuberculous infection so that reinfection will result in lesions of primary type, is uncertain. We have observed several instances of the development of infection and lesions in persons who are either known to have lost their sensitivity or who may be assumed to have done so because they have typical calcified primary complexes. Although the number observed is too small to permit any conclusion as to the relative frequency of lesions anatomically characteristic of primary type and reinfection type disease, the several histories cited show that both types may occur.

Among Negroes with lesions typical of primary tuberculosis in childhood, there are striking variations in the clinical course. The cases here reported show that two patients may have lesions which are virtually indistinguishable in the X-ray film, both appearing as scanty pulmonary infiltrations with massive lymph node enlargement, and yet one patient may have fulminating disease, rapidly fatal, while the toxaemic symptoms of the other may gradually disappear, with later retrogression and clearing of the lesion.

Similarly among patients who developed pulmonary infiltrations without roentgenologically demonstrable adenopathy, there was no uniformity of clinical response. It is apparent that lesions indistinguishable in site and roentgenological appearance may in one instance progress to the formation of cavities and in another instance promptly retrogress and scar, and it is evident that there are no certain clinical or roentgenological criteria for distinguishing these primary lesions from infiltrations developing in patients long known to be reactors to tuberculin.

The wide variation of opinion among European investigators (11) as to the frequency of hilar lymphadenopathy in primary lesions of adolescents, suggests that the presence or absence of lymphadenopathy

may be largely dependent upon racial and constitutional differences. Pertinent in this connection are the studies of Lurie, who has reproduced acute disease with tracheobronchial lymph node enlargement by a single exposure to a known quantity of naturally inhaled bacilli in a susceptible strain of rabbits and chronic pulmonary disease without adenopathy by a single similar infection of rabbits of a resistant strain (12, 13). It is possible that in man, also, variations in type of disease dependent upon the presence of reinfection are overshadowed by the variations due to racial and constitutional differences. Scheel's (4) comment that it is probable that "childhood type" and "adult type" lesions are only two isolated examples of a multitude of forms that primary infection can take, is worthy of consideration. As we have pointed out, it is impossible to distinguish primary from reinfection lesions in adolescents by roentgenological appearance and clinical examination alone. If serial tuberculin tests have been performed at intervals of three to six months, distinction can be made in some instances. In our experience, however, as well as in the recorded experience of others (3), the majority of tuberculous infiltrations appear to develop at least a year after the last negative tuberculin test. Whether such lesions represent primary or later infection is merely conjectural. In view of all these facts the distinction between primary and reinfection disease will rarely be a useful guide in estimating prognosis or planning treatment in the individual case in the adolescent age period.

SUMMARY

1. Illustrations are given of a wide variety of types of primary tuberculosis in adolescents, with great discrepancy in anatomical character and clinical course, ranging from cases quite like the typical primary tuberculosis of childhood to cases resembling progressive reinfection type tuberculosis in adults. The diagnosis of "primary tuberculosis" in these cases was made by correlation of passage from the tuberculin-negative to the tuberculin-positive state, and the development of X-ray evidence of tuberculous infiltration.

2. Cases of primary tuberculosis in adolescents or adults similar in anatomical and clinical character to typical primary tuberculosis in childhood were not common. They proved more frequent in Negroes than in whites, a fact to be correlated with the greater frequency of lymph node involvement in the Negro in all types of tuberculosis.

3. The material available was not large enough to furnish a basis for

estimating the relative frequency of the different types of primary tuberculosis in adolescents and adults.

4. The wide variety of types observed in the material studied made it clear that among adolescents tuberculous lesions cannot be diagnosed as primary on the basis of roentgenological appearance or clinical behaviour. Actually, the majority of adolescents and adults under our observation who developed tuberculosis did so more than a year after first evidence of infection. It would appear that in adolescent and early adult life, differentiation of tuberculous lesions into primary and reinfection types can be established so infrequently that the practical importance of the distinction is questionable.

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CONTINUOUS ARREST OF LUNG MOVEMENT[1,2]

Treatment of Pulmonary Tuberculosis in an Equalizing Alternating Pressure Chamber

ALVAN L. BARACH

Rest in bed is still regarded as the most effective principle in the treatment of active tuberculosis (Amberson (1), Miller (2)). Webb and his colleagues (3) pointed out that postural rest, in which the patient lies on the affected side, "allows more complete rest in the injured lung and, consequently, favors healing." Small bags of shot up to two pounds have been placed over the upper part of each side of the chest in bilateral apical disease in order to rest the upper lobes and allow the bases to be used mainly for ventilation.

When pneumothorax is used to collapse a tuberculous lung, a considerable excursion of the diseased lung continues to take place with each respiratory cycle (Pinner (4)). Pinner and Rubin (5) have recently emphasized that pneumothorax is not a substitute for natural healing but that it "aids the healing process as the result of the relaxation and diminution in volume of the diseased lung and the reduction of its functions. A caseous pneumonic process in a person with poor resistance will ulcerate and spread under pneumothorax as readily as if the lung were not collapsed. In many respects a person with pulmonary tuberculosis whose disease heals spontaneously is more fortunate that one who requires the help of collapse measures."

Our intention in quoting the above remarks is not to minimize the importance of pneumothorax and other collapse measures in the treatment of pulmonary tuberculosis, but to report expert opinion that the clearing of the inflammatory tuberculous process, the ultimate objective of therapy, is aided by a decrease in the functional activity of the lung, namely, rest of the diseased organ. The method employed in this investigation adds to general body rest a new type of local lung rest in which excursion of the lung margins is not measurably present. It

[1] From the Department of Medicine, College of Physicians and Surgeons, Columbia University, and the Presbyterian Hospital, New York City.

[2] This investigation was supported by a grant from the Mary W. Rumsey Fund.

involves considerable coöperation on the part of the patient and the use of a special apparatus. On the other hand, it is free from the risk and the complications of collapse therapy, and it may be employed in types of disease in which pneumothorax cannot be used.

In a previous communication (6) the mechanism of alternating pressure respiration was described. It was shown that patients with pulmonary disease treated in a chamber by an alternating pressure of ± 55 mm. Hg., 25 times a minute, as originally suggested by Thunberg (7) for respiratory paralysis, were unable to maintain continuous arrest of lung movement and, furthermore, that compression and expansion of the chest resulted from the positive and negative cycle of pressure, respectively. This was found to be due mainly to the resistance interposed by the tracheobronchial tree to the passage of air in and out of the lung. By artificially creating a similar resistance to the air pressure applied to the chest wall, the pressures on the inner and outer surface of the thorax were made approximately equal, as well as the pressures applied to the upper and lower surface of the diaphragm. Under these circumstances an adequate ventilation of the lungs was accomplished without voluntary breathing and without discernible movement of the ribs and diaphragm, as far as could be determined through observation and by fluoroscopic and roentgenographic examination (6).

The apparatus employed to accomplish this object was called an equalizing alternating pressure chamber.

The cases treated in this series were patients with advanced pulmonary tuberculosis with cavity, in whom collapse therapy was considered unsuitable because of the bilateral and extensive nature of the disease. Five patients were selected in whom spontaneous resolution of the disease was deemed very unlikely. These patients had been at rest in bed for a period of two to seven months prior to transfer to Presbyterian Hospital for treatment by equalizing pressure. We will present their clinical course during and following residence in the equalizing alternating pressure chamber. Our purpose in restricting the use of local lung rest only to patients with bilateral advanced disease was to determine the range of effectiveness of this method in patients who previously demonstrated little or no resistance to progressive spread of the tuberculous process. If a distinct arrest of the lesion and initiation of a recovery process followed treatment in the equalizing chamber in these cases, it was believed that its use would also be justified in patients with early or less severe disease.

METHOD

The apparatus first employed was the alternating pressure chamber with the inner box (6). At a pressure of ± 50 to 55 mm. Hg., when an equalizing pressure of 5 cm. of water was used, there was a tendency toward a slight hyperventilation. As seen in the table of the blood gases introduced later in the paper, a decrease of arterial carbon dioxide takes place with an elevation of the arterial oxygen saturation after two hours of equalizing pressure. In the animal experiments previously reported (6), alternating pressure alone does not produce as efficient ventilation as when it is combined with equalizing pressure. It should therefore be kept in mind that hyperventilation may occur, and that only such air movement as is required to stop voluntary respiration is advisable.

The equalizing pressure that was found most satisfactory was between 5 and 6 cm. of water. This corresponds approximately to the lag in pressure found experimentally in the intrapleural cavity (6). In the first patient, 4 cm. equalizing pressure was used, which was probably not always adequate to stop the impulse to breathe. In the other cases, the pressure applied to the chest wall fluctuated between 5 and 6 cm. less than that present at the nose. The degree of pressure difference exercised by the inner box was modified by varying the size of the various holes on its top and side. All patients were treated in the alternating chamber with the inner box. The fifth patient was also treated for one month in the transportable equalizing pressure chamber. In the latter, a partition between the head and body end contained a sponge rubber collar which fitted around the neck. The rotary compressor forced air into the head compartment and thence by an external communicating tube to the body portion of the chamber. A gate-valve in circuit regulated the differential pressure between the head and body compartments. It was found that the same decrease in pressure applied to the chest was required by this method as by the larger chamber, in order to equalize the resistance of the tracheobronchial tree.

The psychic influence of the larger chamber was reassuring to the new patient as either a doctor or nurse sat with him at the beginning of treatment. In the transportable chamber the entire body is wheeled into the chamber and the metal door locks him in at the head end. Obviously, this procedure would challenge patients with claustrophobia. The physician would then be called upon to reassure the patient, or to stress the value of the therapeutic objective. The one sense of discomfort is the sensation of the ear drums moving in response to variations

in pressure. It is important to inform the patient that the feeling will be like that experienced in going up and down an elevator swiftly. At first this sensation is conspicuous and in some instances painful. However, in all the patients treated, and in the author, it was a sensation that disappeared from consciousness in the course of the first hour or two. When one first goes into the chamber, the ear sensation recurs again but in the course of several days it is quickly forgotten. At times the sinuses are the seat of feelings of discomfort due to air pressure variations. Several drops of 1 per cent neosynephrin in each nostril at the start of treatment has occasionally been used, especially if a slight cold is present. In the transportable chamber, a speaking box allows the patient to communicate freely with the physician (or technician or nurse). At the beginning of treatment, it is reassuring to have someone around. Our fifth patient, after the first day, was in the room alone, and was quite content to pull a string in the chamber which rang a bell at the nurse's station. The sixth case, not included in this series, has been successfully treated for two months in the transportable chamber, without previous residence in the larger chamber.

The pressure variations were discerned by a mercury manometer made of three-quarter inch glass tubing. If the pressure were to increase above the desired level, the light from a photoelectric cell would be interrupted and the compressor stopped. A gauge was also placed above the chamber which registered the pressure change on a dial. It would be simpler to have a contact point about 5 mm. Hg. on each side of the desired pressure, as noted on the face of the dial; if the pressure would get beyond the range selected, an electrical impulse would be transmitted to the compressor and stop it.

The *equalizing* pressure was registered by a calibrated gauge placed in the head compartment. In addition to the speaking box, the head compartment contained a radio-speaker.

At the start of treatment the patient is put on a stretcher on wheels and wheeled into the chamber. The partition is put in place and the patient's head slipped through the collar. Pillows are introduced under his head and the door swung shut and tightened. The motors are turned on and respiration by voluntary control is soon dispensed with. The patient is instructed to stop breathing at the end of a normal expiration. The elastic tension of the lungs is less in this cycle than it is during the inspiratory phase. Furthermore, cessation of breathing and of chest movement are empirically easier to obtain. At the commencement of

treatment, the patient from time to time avails himself of a normal breath but as time goes on he feels no necessity to do so. Observation of the chest generally reveals no movement. Any clothing which the patient wears will naturally change its position, and there may even be some alteration of the contour of a fleshy individual without indicating lung movement. The abdomen shows fluctuation in volume, varying with the amount of gas in the intestine or stomach. It will be apparent that gas in a relatively closed space will vary in volume, coincident with changes in pressure; however, the movement of the abdominal surface does not connote movement of the diaphragm since the pressure in the abdomen is reflected against the lower surface of the diaphragm and it is there counterbalanced by similar pressures on the upper surface of the diaphragm. This takes place whether compressable gas is in the intestine or not, since compressed gas immediately reflects the original pressure on the surface of the abdomen.

The temperature is regulated according to the comfort of the patient, generally between 68° and 72°F. In the transportable chamber, brine was used in copper pipe beneath the floor of the chamber; circulating ice water could be employed, as was done in the small room.

The duration of treatment each day was six hours in the first patient. In the others, the patient was in the chamber from 9.00 a. m. to 12 noon. He was taken out for lunch and dinner, generally also for milk and orange juice at 4.00 p. m. At 10.00 p. m. he was removed to his bed and soon went to sleep. If he was unable to fall asleep easily a capsule of nembutal or sodium amytal was prescribed. He was thus exposed to local lung rest for twelve to thirteen hours daily. In most patients, treatment was omitted on Sundays, although in the fourth and fifth patients, and in the second course of the third patient, treatment was given on Sundays for eight hours. It is probably better to allow Sunday as a day without treatment in order to have the patient make whatever social contact he desires. It is also a break in a treatment which would appear to be monotonous. Of psychological interest is the fact that more complete body rest is made possible as a response to cessation of voluntary respiration than is ever noticed in patients at bed-rest. This is not simply due to the confined position which the inner box or transportable chamber indicates, but is a sequence of a certain relaxation of consciousness that follows equalizing pressure respiration. The absence of all effort on the part of the respiratory musculature evokes a subjective attitude that is decidedly different from ordinary bed-rest.

Two of the patients spontaneously offered the statement that they felt as if they were "in their mother's belly." However, despite the long periods in which they lie without movement and seemingly without effort, there are times in which they wish diversion. A radio has been made use of mainly. Occasionally, moving pictures have been shown them. Short periods of conversation appear to be helpful when the patient is taken out for meals.

The duration of treatment has been arbitrarily set at about three months. It will be realized at once that this period of treatment was not intended as the length of time in which complete healing would take place, but, rather, that a recovery process might be initiated which would then continue after this therapy was replaced by ordinary bed-rest. This method of treatment, which supplies local lung rest, is based naturally on the thesis that inflammatory lesions, including those of tuberculosis, are more susceptible to healing when movement of the affected part has ceased. It is acknowledged that joint tuberculosis heals more readily with local immobilization than it does with simple bed-rest. If the mechanism of healing of tuberculous pulmonary disease is facilitated by a type of immobilization of the lung which we have described, it seemed also likely that such healing once begun might continue even without continuance of local lung rest, if other measures such as mental and body rest were also provided.

The attempt was made to give the patients a hygienic-dietetic regimen. The regular ward diet of the hospital was provided with extra helpings if desired; the patient was encouraged to eat plentifully but never under pressure. In-between feedings of milk or orange juice or both were offered, generally at half past three in the afternoon, and occasionally in the middle of the morning, if they did not interfere with lunch. Increased vitamin intake was administered. The last three patients were also given vitamin-B complex in capsules.

The patients were allowed bathroom privileges, they washed themselves, except the fourth patient who was too weak to do so. Smoking one or two cigarettes after meals was allowed if desired. However, no physical examination was permitted except the one on admission and departure. The practice of limiting physical examinations to a minimum was to prevent the possibility of excessive lung movement; coughing to raise sputum was considered desirable, but repeated coughing without expectoration was discouraged.

A sputum cup was provided alongside the patient's head. Some

patients coughed during the positive cycle; others did not notice any difference in the ease of coughing in either cycle. The decrease in coughing was one of the earliest effects of equalizing pressure.

The blood gas determinations were done by the method of Van Slyke and Neill (8).

CASE REPORTS

Case 1: Male, age twenty-six years, had no history of exposure to tuberculosis. Born in U. S., moved to Poland at six months of age, and returned to U. S. nine months ago. He worked in a factory in Poland in which white dust was in the air, type unknown. For many years cervical lymph nodes became swollen for two to three days at a time, but never broke down.

His present illness began one year prior to present admission. Patient developed a productive cough while he was in Poland. Three months later, in New York, loss of weight, fatigue and night sweats began. He was admitted to a city hospital two months later and was at bed-rest for seven months. During this time he had two haemoptyses, ran a persistent fever, at times from 100° to 103°F., alternating with periods of lower fever. During the first three months of bed-rest he gained weight from 139 to 146 lbs. From then on his course was slowly but steadily downhill and during the following four months his weight declined to 132 lbs. On this first admission, X-ray films of lungs showed diffuse nodular infiltration with a cavity in the right upper lobe and infiltration of the left upper lobe. Subsequent films show a spread of the process in the right upper lobe and a new cavity in the left upper lobe. He was then transferred to Presbyterian Hospital.

Physical examination showed a fairly well developed but poorly nourished male of twenty-six years, who looked pale and chronically ill. He coughed occasionally and raised thick, yellowish mucopurulent, blood-streaked sputum. There were amphoric breath sounds at right top, anteriorly in infraclavicular region and posteriorly and medium moist râles at the right top, in the right axilla, left apex and left axillary line. Impaired resonance was present from apex into cardiac dulness anteriorly and from apex almost to base posteriorly. Over these areas were bronchovesicular breath sounds, slightly increased voice and whisper sounds.

X-ray examination of chest showed mottled and rarified shadows in the middle two-thirds of the left lung field and upper two-thirds of the right lung field. A large cavity was seen at the level of the right second rib anteriorly and smaller cavities in the left second interspace anteriorly and left fourth rib anteriorly. Below the large cavity on the right, diffuse productive shadows extended into the right lower lobe.

The blood count was normal, except for 11,300 white cells with 69 per cent polynuclear cells. Sputum was positive for tubercle bacilli. Sedimentation

rate was 35 mm. in one hour. Gastrointestinal X-ray films suggested duodenitis or duodenal ulcer.

Patient was treated in the equalizing pressure chamber, with a differential pressure of +4 cm. water in the positive phase, for two months, six hours daily, six days in each week. Maximum weight gain was 12 lbs. from 132 to 144 lbs. Sedimentation rate was 15 mm. in an hour at the end of treatment. Temperature averaged between 98° to 99.6°F. His pressure therapy was complicated by attacks of abdominal pain requiring a Sippy regimen for duodenal ulcer or duodenitis. The cough and sputum decreased.

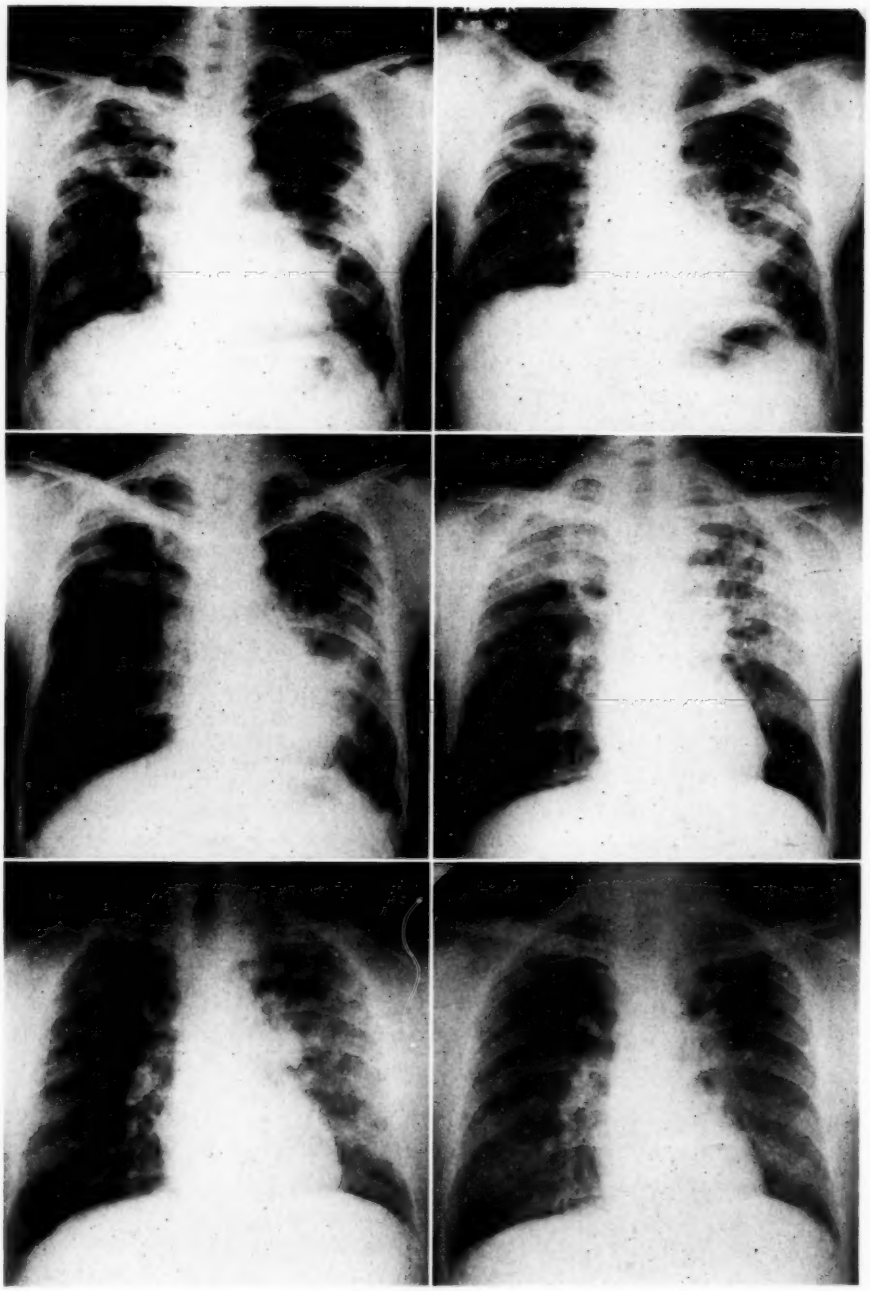
X-ray pictures showed a gradual clearing of the mottled shadows below the cavities, especially in the left lung field. No change in size of cavities was observed. (See figures 1, 2 and 3.)

The patient was transferred back to the city hospital where unsuccessful attempts were made to collapse first the right lung and later the left lung. (See figures 1, 2 and 3.) The patient now visits a city convalescent out-patient department. His general condition was said to be fair, and prognosis for ultimate recovery unfavorable (at this writing, two years after patient left Presbyterian Hospital).

Comment: The patient seemed clinically better following two months of equalizing pressure treatment for six hours a day. The equalizing pressure of 4 cm. water in this case may not have been adequate to arrest lung movement completely, as it was found that 5 to 6 cm. was required in subsequent cases. Nevertheless, the patient had shown a progressive downhill course prior to equalizing pressure treatment. His fever which had averaged from 98° to 102°F. previously was consistently lower, between 98° and 99.6°F. He made a maximum weight gain of 12 lbs., there was a decided decrease in cough and expectoration and the sedimentation rate decreased from 35 to 15 mm. in one hour. In addition, the X-ray films both at Presbyterian Hospital and the city hospital showed considerable clearing of the lesions in the left lower lobe. No decrease in the size of the cavities was evident as result of this short period of treatment and the ultimate prognosis is unfavorable, since pneumothorax was unsuccessful.

Case 2: Male, age thirty-eight years with no exposure to tuberculosis. Born in England; in U. S. twelve years. Janitor in office building for twelve years. He had influenza in 1918.

Three years before present admission, patient developed a productive cough. During the last year, sputum increased to six ounces daily, and was occasionally streaked with blood; night sweats began and he lost twelve pounds in weight.



FIGS. 1-6

FIG. 1. (Upper left) Case 1. At start of equalizing pressure treatment after seven months' bed-rest.

FIG. 2. (Upper right) Case 1. After two months' equalizing pressure treatment.

FIG. 3. (Center left) Case 1. Attempted collapse of right lung three weeks later.

FIG. 4. (Center right) Case 2. Before equalizing pressure.

FIG. 5. (Lower left) Case 2. After four months' equalizing pressure treatment.

FIG. 6. (Lower right) Case 2. Eleven months after equalizing pressure treatment.

He was at a city hospital for one and a half months, where he had a low-grade fever of 99° to 100°F., at times 101°F.; the sputum decreased to two to three ounces daily, and there was a gain in weight of four and a half pounds on bed-rest.

Examination of the larynx after hoarseness had been present for two weeks showed slight redness and slight oedema of the epiglottis. The arytenoids were very thickened and oedematous and slightly reddened. Diagnostic impression: tuberculosis of the larynx.

There were dulness and loud bronchial breathing at the right apex with consonating râles and medium moist râles after cough and dulness with bronchovesicular breathing and many loud consonating and medium moist râles at the left apex and some at the base.

X-ray examination showed productive infiltration throughout both lungs and dense infiltration on the right with several cavities above the second rib and many small cavities in the upper half of the left lung field, surrounded by an exudative reaction.

Patient was transferred to Presbyterian Hospital. Physical examination showed a fairly well developed and nourished man of thirty-eight years. Physical signs in the lungs and the X-ray examination were as noted in the city hospital record above.

Sputum was positive for tubercle bacilli. Blood count: Haemoglobin 90 per cent; red cells 5,200,000; white cells 8,000; polynuclears 57 per cent; sedimentation rate 59 to 75 mm. in one hour.

Patient resided in the equalizing pressure chamber twelve hours daily, six days a week for four months. A differential pressure of +6 cm. was used.

Cough became infrequent and sputum decreased to 4 cc. daily. After nine weeks' treatment, temperature became flat and stayed normal from then on. Weight gradually increased to 157 lbs., a gain of 35 lbs. in four months. Sedimentation rate gradually decreased to 17 mm. in one hour. Hoarseness gradually disappeared in two months, when larynx was found to be normal.

During the previous two months in the city hospital, X-ray films showed no improvement. After seven weeks in the chamber, clearing began and gradually increased, with marked lessening of infiltration in both lung fields, as seen by comparison of films on admission and after four months' equalizing pressure treatment.

Chest examination, then, showed fine crepitant râles over upper two-thirds of left lower lobe posteriorly and in the left axilla.

Patient was returned to the city hospital, the sputum then still positive, and after four months, he was transferred to a convalescent sanitarium, where the sputum was consistently negative for the entire five months of his stay. Sputum, on direct and concentrated specimens, has continued to be negative on ambulatory activity for seven months since his discharge from the sanitarium.

Eleven months after treatment in alternating pressure chamber, X-ray examination showed striking resolution, leaving behind small central foci with linear fibrosis. The degree of change may be observed in the accompanying reproductions of X-ray films taken before and after treatment. (See figures 4, 5 and 6.) Lungs were clear except for a few fine râles at the right base.

SEDIMENTATION RATE AND BODY WEIGHT
OF A PATIENT DURING RESIDENCE IN
EQUALIZING PRESSURE CHAMBER.

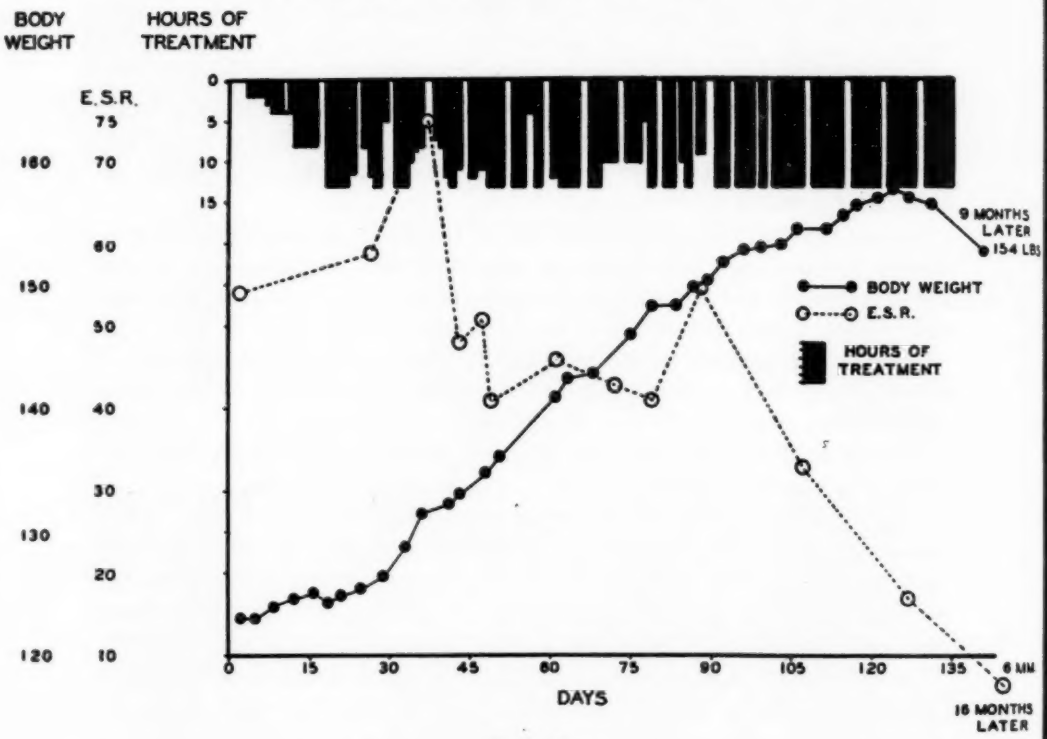


CHART 1

The gradual weight gain and decrease of sedimentation rate are shown in chart 1.

Determination of the blood gases before and during residence in the alternating pressure chamber showed no significant change. (See table 1.)

Comment: This patient had far advanced pulmonary tuberculosis with many small cavities in both lungs and tuberculosis of the larynx. The X-ray pictures of the lungs had not shown improvment, the physical

signs in the lungs did not change and fever continued during the bed-rest prior to the use of the equalizing pressure chamber. After four months of local lung rest, the clinical improvement was marked by: (*1*) gain of 35 lbs., (*2*) disappearance of fever, (*3*) marked decrease in cough and diminution in sputum from 60 to 4 cc. daily, (*4*) marked marked decrease in inflammatory process, as shown by X-ray examination, (*5*) sedimentation rate decreased from 75 mm. in 1 hour to 17 mm., (*6*) larynx became normal in appearance, (*7*) decrease of physical signs

TABLE 1

Arterial blood gases in patients treated in alternating equalizing pressure chamber

CASE NUMBER	OXYGEN CONTENT	OXYGEN CAPACITY	OXYGEN SATURATION	CO_2 CONTENT	pH	REMARKS
	vol. per cent	*vol. per cent*	*per cent*	*vol. per cent*		
1	18.6	19.2	97.9	52.6		Rest in bed
	18.4	19.5	94.4	50.5		After two hours' alternating pressure
	18.6	19.7	94.4	50.6		After five hours' alternating pressure
2	17.1	18.0	95.0	46.9	7.40	Rest in bed
	16.7	17.6	94.9	48.7	7.39	After seven hours' alternating pressure
3	18.0	19.4	92.8	47.0	7.53	Rest in bed
	18.5	19.2	96.4	51.1	7.40	Rest in bed
	20.3	21.4	94.9	52.0		Rest in bed
	20.6	20.6	100.0	48.5		Immediately after two hours in equalizing pressure
	20.1	19.2	100.0+	44.9		Single determination after two and one-half hours in equalizing pressure
4	11.2	12.5	89.6	56.6		Rest in bed
5	20.9	21.6	96.8	49.6		Rest in bed

in chest, and (*8*) continuation of improvement after four months' treatment, with negative sputum now for one year on ambulatory activity. Clearing of infiltration and cavities took place in both lungs, with persistence of small residual foci and linear fibrosis. On physical examination lungs were essentially clear, except for a few fine râles at bases.

Case 3: Male, age thirty-one years with no exposure to tuberculosis. He had bacillary dysentery in 1928.

His present illness began nine months ago when the patient caught cold and

had a nonproductive cough with general malaise. Symptoms did not change markedly until three months later when the cough became pronounced and produced one-fourth to one-half cup of sputum daily. There was never any haemoptysis. At this time he noticed easy fatigability and one flight of stairs produced dyspnoea. He suffered from night sweats, alternate chills and fever and progressive weight loss, totaling 18 lbs. at the end of six months' illness. He then entered a city hospital where he continued to run a daily fever of 100° to 101°F. Examination at this hospital revealed positive sputum, infiltration and cavitation in the upper halves of both lungs. During a period of two and one-third months of bed-rest, cough, expectoration and fever continued. Sputum was about 40 cc. daily. There was a weight gain of 2 lbs. It was noted on the hospital chart at one time that slight symptomatic improvement had occurred and at another time that no symptomatic improvement had taken place. The X-ray pictures were reported to have shown "questionable improvement both sides".

Physical examination revealed a thin man of thirty-one years who appeared chronically ill. There was dulness from the apex to second rib and sixth dorsal spine on the right with bronchovesicular breath sounds and increased voice sounds and many moderately coarse râles.

Tactile fremitus, vocal fremitus and breath sounds were increased to the second rib and dulness to the third rib and sixth dorsal spine and fourth dorsal vertebra on the left. There were many moderately coarse râles to the fourth rib and dorsal spine.

Stereoscopic films of the chest showed an oval cavity at the level of the right second interspace measuring about 2.5 cm. in a vertical direction and about 1.5 cm. transversely, with a smaller area of diminished density measuring 1.4 cm. in diameter just below it. Surrounding and beneath the cavities, shadows suggesting inflammatory exudate were present over the upper half of the right lung. On the left side a cavity is present near the anterior chest wall at the level of the third rib in front which measures 2 cm. in diameter. There is also an oval area of diminished density at the level of the left first interspace in front which looks like a multilocular cavity measuring 1.7 by 1.2 cm. The upper three-fifths of the left lung shows shadows suggesting inflammatory exudate. These are especially marked in the mid-lung field where a cavity may also be present. Sputum was positive for tubercle bacilli. Sedimentation rate was 50 mm. at the end of one hour.

At the end of six weeks the temperature became normal and remained normal. The patient had gained 17.5 lbs. and the sputum decreased to 20 cc. daily. Following a two weeks' period without treatment for investigation of nausea, a three and one-half weeks' residence in the equalizing pressure chamber was followed by increasing strength, very infrequent cough and decrease of sputum to 4 cc. daily. The sputum was positive in one of eight

examinations. The sedimentation rate decreased to 13 mm. in an hour. (See chart 2.) At the end of ten weeks' residence in the equalizing pressure chamber the two areas of diminished density in the right lung were not visible on the films taken at this time. The cavity near the left anterior chest wall at the level of the third rib in front which measured about 2 cm. in diameter was not seen on the later films. The multiloculated cavity described above was replaced by a small round area measuring 1.2 cm. in diameter. There was a

SEDIMENTATION RATE AND BODY WEIGHT OF A PATIENT DURING RESIDENCE IN EQUALIZING PRESSURE CHAMBER.

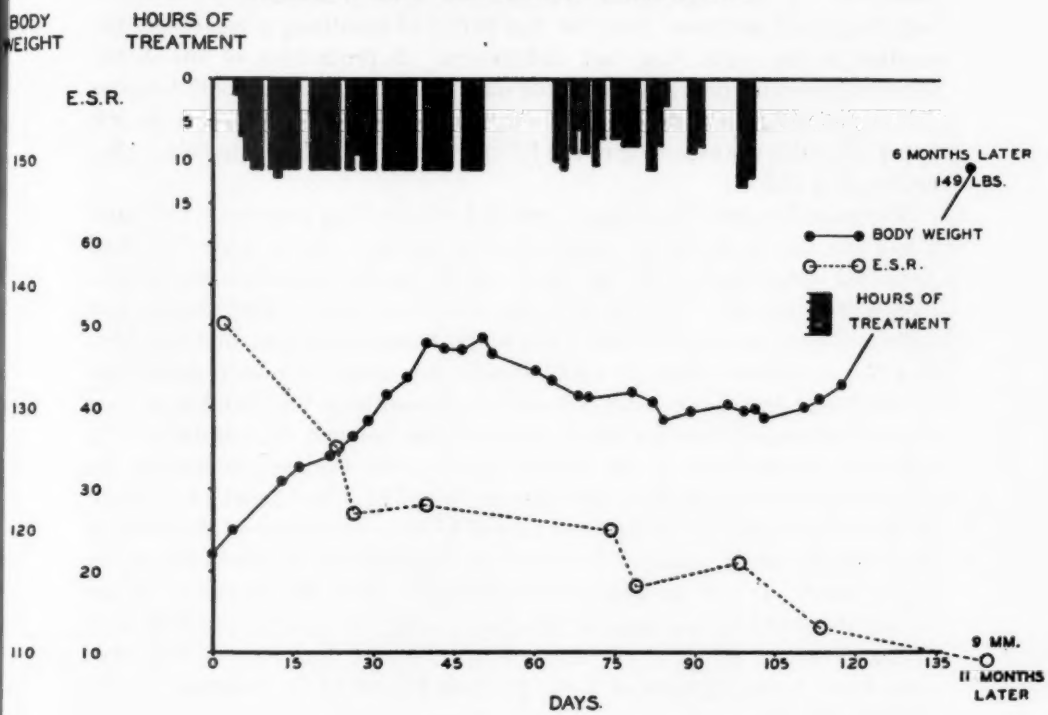


CHART 2

definite diminution in the shadows suggesting inflammatory exudate in both lungs, the change being especially marked in the right upper lobe.

The patient was transferred back to the city hospital from which he had come, then sent to a convalescent sanitarium for five months, and again returned to the city hospital for study.

He looked well nourished, was afebrile, coughing about half a dozen times daily, and would raise about 30 cc. of heavy sputum, which was positive.

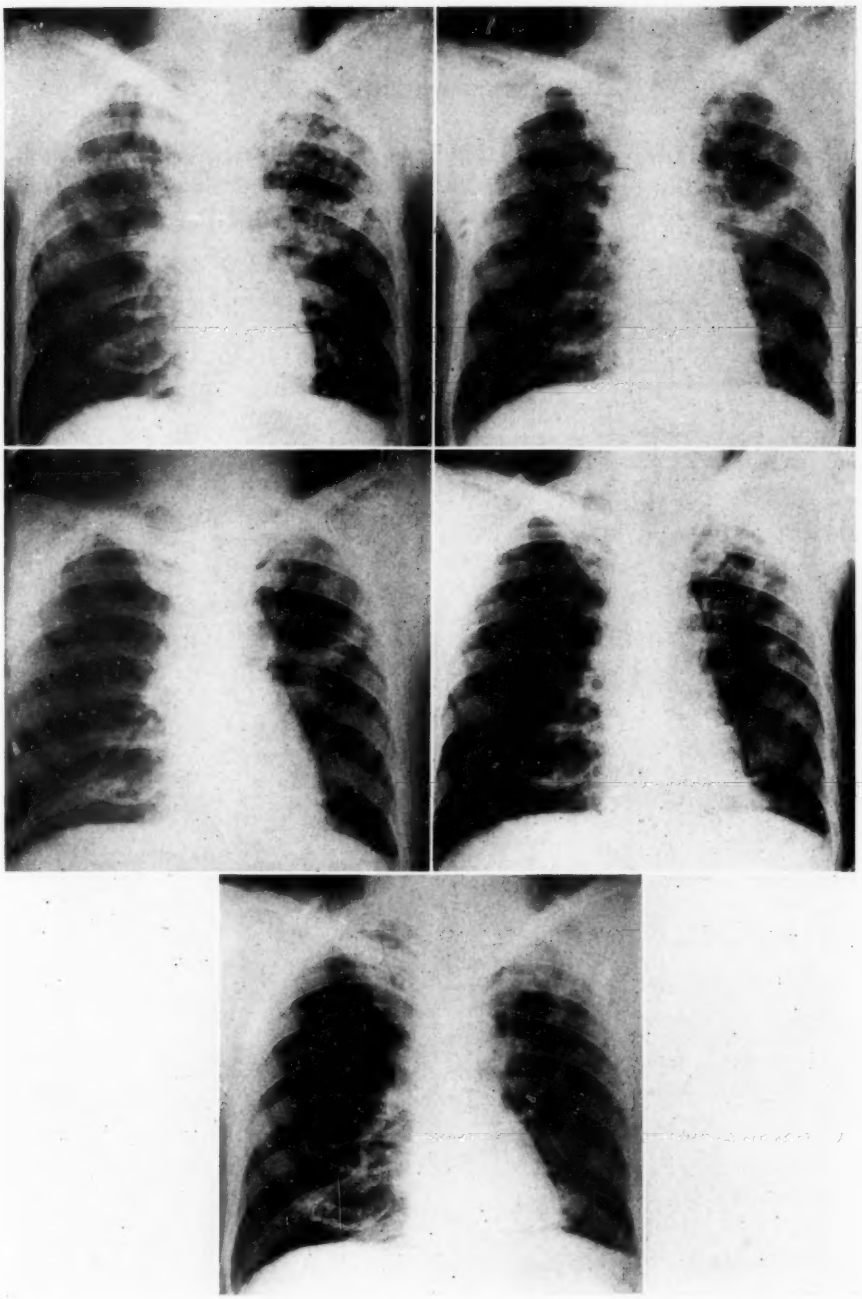
After five weeks' rest in bed, an X-ray film showed no appreciable change on either side.

The patient was then admitted to Presbyterian Hospital to see whether a second period of treatment with equalizing pressure would exercise a beneficial influence on the remaining cavity in the left upper lobe. X-ray pictures on this readmission showed this cavity to be 2.4 by 3.0 cm. in width and of considerable depth as revealed by planigraphic X-ray films. No cavity was present on the right side in stereoscopic and planigraphic films. Before the patient was transferred to the convalescent sanitarium six months previous to his present admission, this cavity was represented in the film by a small round area 1.2 cm. in diameter. The decrease in the inflammatory exudate in both lungs had continued since the first period of equalizing pressure and the cavities in the right lung had disappeared. Reproduction of the X-ray pictures illustrate the resolution of the inflammatory exudate of both lungs as well as the disappearance of cavities in the right upper lobe and in the left upper lobe with the exception of the 1.2 cm. cavity in the left lung field. (See figures 7, 8 and 9.)

The second course of treatment consisted of equalizing pressure for two and a half months, twelve hours daily, six days a week. His weight which had decreased from a high of 149 lbs. before transfer to the sanitarium, to 131 lbs., increased to 139 lbs. Sputum diminished to 4 cc. daily. Temperature and sedimentation rate were normal. The lungs showed fewer râles on both sides. The X-ray pictures after six weeks showed the cavity definitely diminished in width and depth, and, after two and a half months in the chamber, its size was approximately one-fourth to one-fifth the volume on admission. In addition, retrogression of the nodular lesions were evident, as seen in the accompanying photographs. (See figures 10 and 11, also 12 and 13.) Comparison of planigraphic X-ray films 12 and 13 show the extent of shrinking of the cavity in the left upper lobe which took place after eleven weeks of equalizing pressure. It will be remembered that this cavity had increased in size during the previous five months' bed-rest, as may be seen by comparison of X-ray pictures 9 and 10. The decrease in volume of the cavity on lung rest, also shown by comparison of X-ray pictures 10 and 11, is confirmed by the planigraphic films.

Case 4: Colored male, age forty-five years with no exposure to tuberculosis. He had dry pleurisy nine years ago. Tonsillectomy was done four years previously. Wassermann negative four years ago, positive (4 plus) three years later. He received twenty-one intravenous treatments.

One year ago patient began to feel weak and tired, losing weight. Ten months before admission, cough, expectoration of 100 cc. of mucopurulent sputum and night sweats occurred. Six months ago, hoarseness and dyspnoea



FIGS. 7–11

FIG. 7. (Upper left) Case 3. Before equalizing pressure treatment.

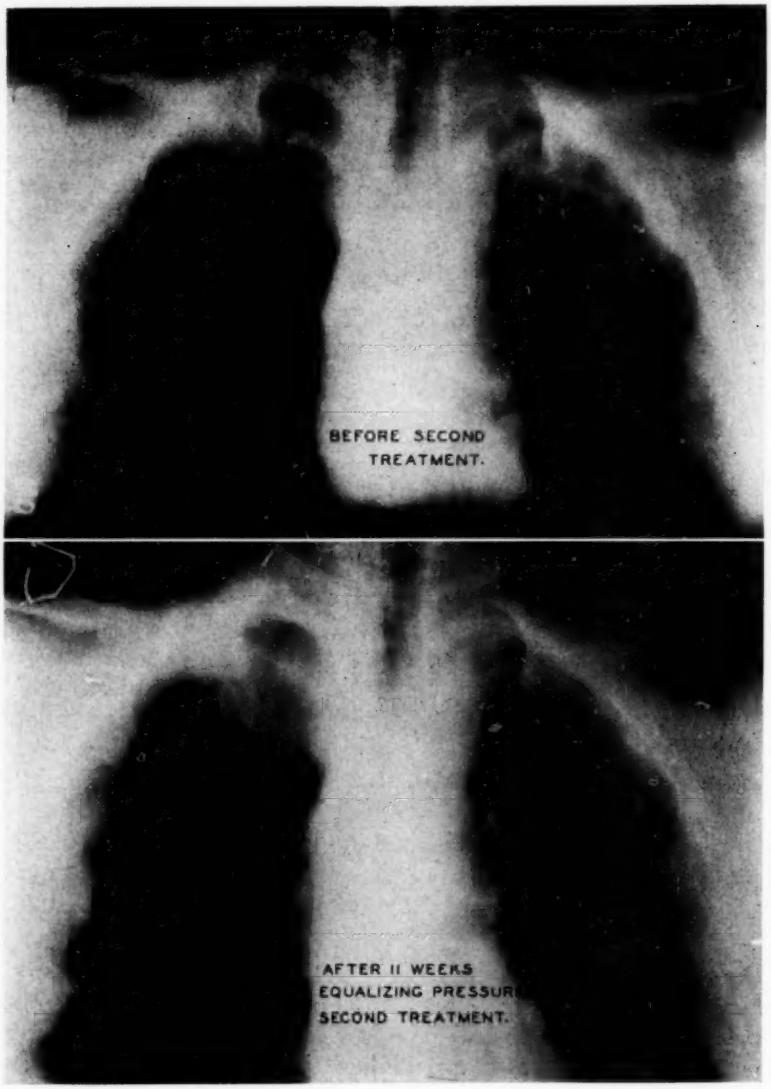
FIG. 8. (Upper right) Case 3. After three and one-half months' equalizing pressure treatment.

FIG. 9. (Center left) Case 3. Five months after equalizing pressure treatment.

FIG. 10. (Center right) Case 3. One year after equalizing pressure and before second course of equalizing pressure.

FIG. 11. (Lower center) Case 3. After eleven weeks of equalizing pressure. Second treatment.

appeared; a tracheotomy was done, followed by removal of a subglottic tumor of the left vocal cord. X-ray films at that time showed shadows at the left apex.



FIGS. 12 AND 13

FIG. 12. (Upper) Case 3. Planigraphic X-ray of cavity in left upper lobe at 9 cm. from table, before second treatment.

FIG. 13. (Lower) Case 3. After eleven weeks' equalizing pressure. Second treatment.

Three months ago he entered a city hospital with a fever of 100° and 101°F. During the previous seven months his weight fell from 140 to 121 lbs.

His course was progressively downhill. His temperature increased from a range of 100° to 101°F., to a range of 101° to 104° and 105°F. At the end of three months of bed-rest he became more toxaemic and was dyspnoeic at rest. X-ray films at three to four weeks' intervals showed continual spread of the tuberculous process with excavations forming in both lungs. The marked extension of the process may be seen in the accompanying films. (See figures 14, 15 and 16.) His weight continued to fall from 121 to 104 lbs. Sputum increased to one and one-half cups daily. Laryngoscopy revealed a moderately reddened and thickened epiglottis; both arytenoids were pallid, oedematous, pear-shaped; left true cord was ragged as a result of old and recent ulcerations. Both cords were reddened and thickened, moved well on phonation but approximated poorly. He was transferred to Presbyterian Hospital to determine the effect of equalizing pressure on his clinical course.

Patient was an emaciated, dyspnoeic, colored male of forty-five years. Over the right lung dulness was present over the right upper and middle lobes anteriorly and posteriorly with fine and medium moist râles. Over the left lung dulness was present over the upper lobe with amphorix breath sounds at the apex and numerous medium moist râles throughout. His sputum was positive. The sedimentation rate was 75 mm. in one hour. Haemoglobin 66 per cent; red cells 3,400,000; white cells 8,600 with 63 per cent polynuclears. By X-ray the lungs show an extensive tuberculosis involving both lungs. The lesions are more advanced on the left side and in the right upper lung field. A number of small translucent shadows are seen in both upper lung fields, one of which is in the left apex and measures 3 cm. in diameter. Another is in the first interspace, which measures 1.5 cm. wide and 2 cm. long. The hilar markings are accentuated.

Patient was observed for four days, during which time his temperature oscillated between 100° and 104°F. He was extremely toxaemic and weak. At this time he was put into the alternating pressure chamber, the equalizing pressure being set at 6 cm. of water. His temperature began to assume a lower level immediately and at the end of one week fluctuated between 97.6° and 100.4°F. His temperature continued to remain at a lower level than it was on admission or at the city hospital prior to admission, at times rising to 101° or 102°F., but it was frequently as low as 100° and 100.6°F. The character of the temperature on admission, at the onset of equalizing pressure and on the eighth week may be seen in the enclosed chart. (See chart 3.)

One month after treatment was begun the following X-ray report was made: A striking change has taken place in the mottled shadows in the right upper lung field in that they appear less confluent and less dense than before. The shadows of infiltration in the left side appeared to show a moderate clearing as

TEMPERATURE AND PULSE BEFORE AND DURING RESIDENCE IN EQUALIZING PRESSURE CHAMBER.

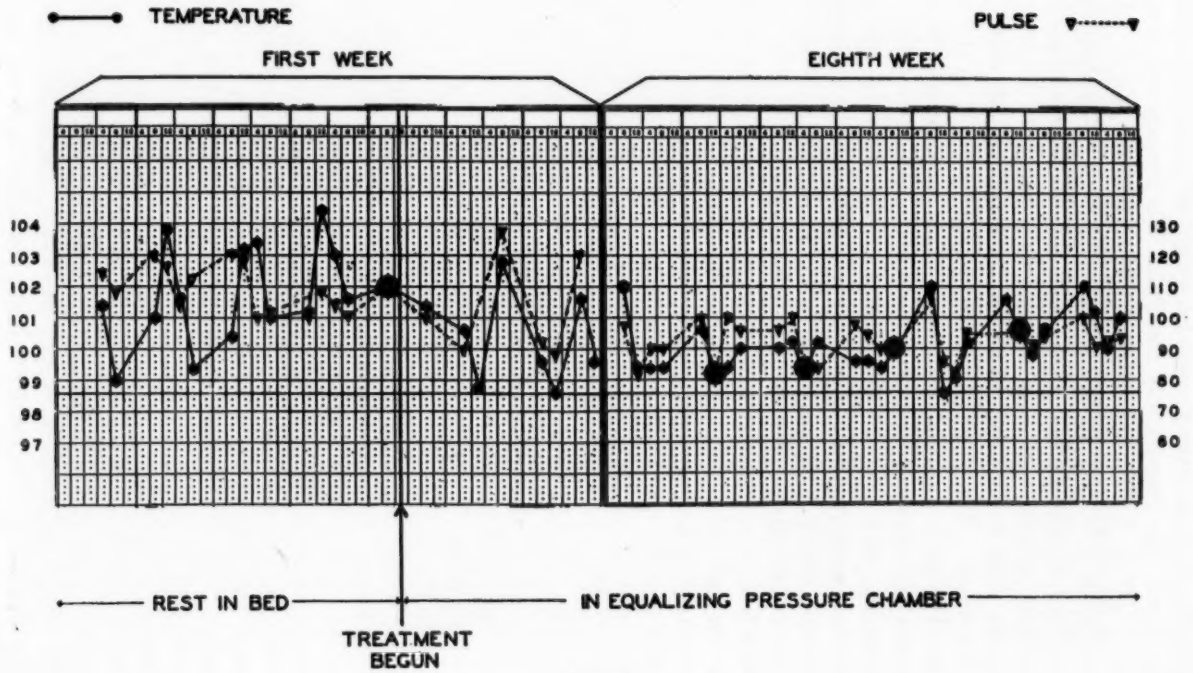
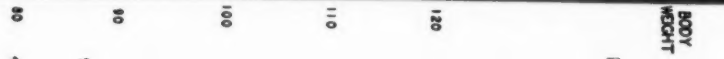


CHART 3



compared to those seen on previous films. X-ray films taken two and three weeks later confirmed the previous notation of clearing in the right upper lung field. In fact, in the admission film it appeared that a cavity was present in the right lung and on the later films this could not be made out. (See figures 15, 16 and 17.) Clinically, at this time the patient was distinctly improved. Instead of having to be carried into the chamber he felt strong enough to walk

SEDIMENTATION RATE AND BODY WEIGHT
OF A PATIENT DURING RESIDENCE IN
EQUALIZING PRESSURE CHAMBER.

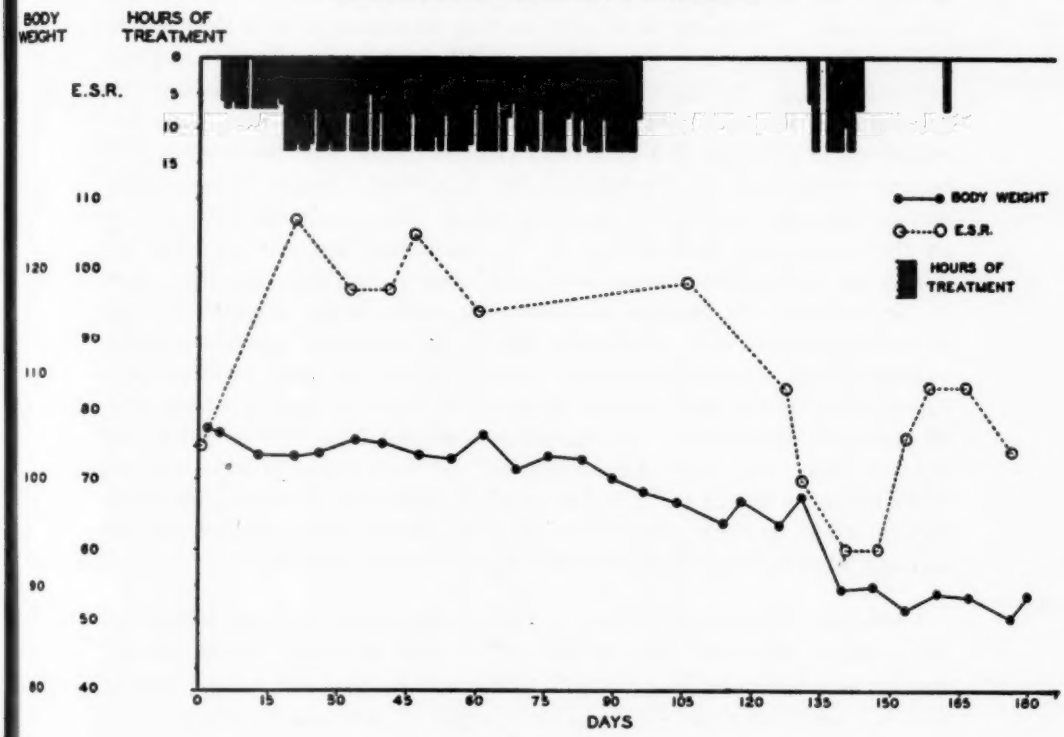


CHART 4

in each time. He lost two pounds in weight in the first two months and his sedimentation time did not diminish. Sputum decreased from 480 to 270 cc. daily. (See chart 4.)

During the ninth week of illness his temperature suddenly began to increase to 103.6°F. with increased pulse and respiratory rates. An X-ray film at this time showed a diffuse shadow of dense consolidation occupying the left upper lung field. (See figure 17.) This suggested tuberculous pneumonia. The

white blood cell count was 11,700 with 80 per cent polynuclears; haemoglobin was 63 per cent; red cells were 3,200,000. He was given sulfapyridine, 4 g. daily for eight and a half days; his temperature abruptly decreased to normal and stayed at a low level until the day when reduction in dosage began. (See chart 5.) He was given a transfusion of 400 cc. of blood because of an increase in his anaemia. This increased his haemoglobin from 41 per cent to 53 per cent and his red count from 2,400,000 to 3,100,000. At the end of sulfapyridine treatment his white blood cells were 21,000 with 83 per cent polynuclears.

The patient was placed in an oxygen chamber with an oxygen concentration of 50 per cent for a period of three weeks, after which he was transferred to a private room. His course from then on was characterized by a slow loss in weight, a persistent fever from 100° to 102°F. and by increased excavation in the left lung. On the twenty-first week of his stay in the hospital, his temperature increased to 102.6° and 103°F. Sulfapyridine was again administered in a dosage of 3 g. a day, with the result that the temperature became normal and stayed normal for ten days when it began to rise slightly despite continued administration of the drug. The results of sulfapyridine on the temperature will be seen in the accompanying chart 6. The response to sulfapyridine suggests that secondary invading organisms were in the cavities. At the end of twenty-six weeks in the hospital, he was allowed to go home, as it was thought that further treatment would be unlikely to influence the course of his disease. His weight at that time was 89 pounds; haemoglobin 52 per cent; red cell count 3,000,000; white count 12,800 with 87 per cent polynuclears. His temperature ranged from 100° to 101°F. for the two weeks prior to leaving the hospital. Patient stayed at home and did fairly well for a month and a half when all his symptoms increased, his cough became worse, he became incontinent to both bladder and bowel movements and was taken to a city hospital where he died three weeks later.

Comment: During the second month of equalizing pressure treatment the patient was distinctly better. The swift downhill course of the disease was temporarily arrested. Although he had not gained weight and his sedimentation rate was still high, he felt much stronger, his temperature was at a lower level and X-ray examination had shown a decided decrease in the shadows of the right lung field. With the acute pneumonitis and the extensive spread of disease in the left lung, it became apparent that further treatment was useless. The response to sulfapyridine was interesting in that it twice was followed by a flat temperature curve for a considerable period. At these times the sputum contained no haemolytic streptococci or pneumococci. *Streptococcus viridans* was the predominating organism. It could not be determined

EFFECT OF SULFAPYRIDINE ON
TEMPERATURE AND PULSE RATE OF
A PATIENT WITH PULMONARY TUBERCULOSIS.

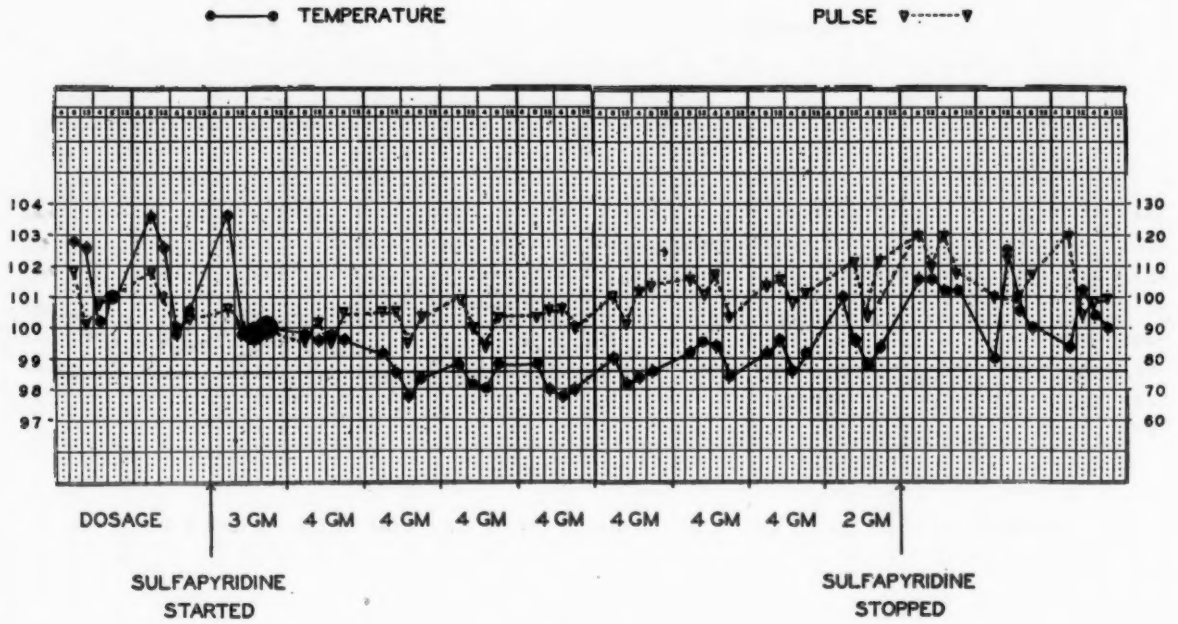


CHART 5

EFFECT OF SULFAPYRIDINE ON
TEMPERATURE AND PULSE RATE OF
A PATIENT WITH PULMONARY TUBERCULOSIS.

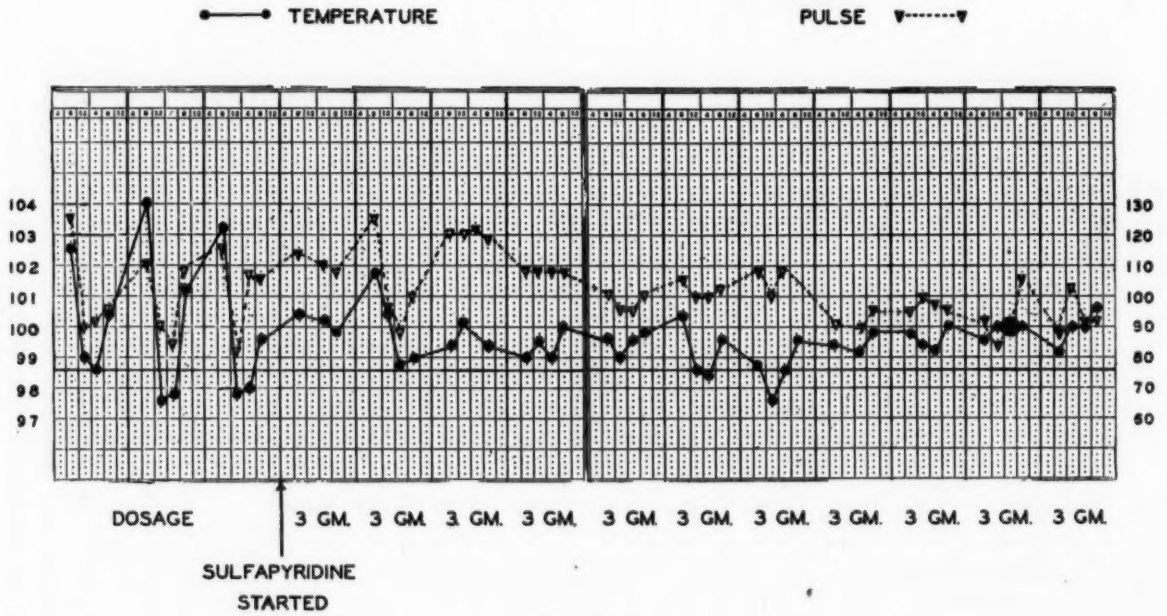


CHART 6

whether the administration of sulfapyridine had any effect on the tuberculous process, but it was considered that the lowering of temperature might have been due to the effect of the drug on secondary invaders rather than on the tuberculous infection itself.

Case 5: Male, age forty-two years. He had drilled rock for two years, five years before onset of symptoms. A renal stone was taken from the left kidney in 1929.

Patient has had known tuberculosis for ten years. At the onset of his disease he developed a cough, fever and weight loss. He had a haemoptysis and X-ray examination showed a cavity in the left upper lobe. During the intervening years he was at five different hospitals for two to seven months at a time. One year ago he had a haemoptysis of six ounces followed by increased cough and expectoration, fatigue, sweats and fever. He had lost fourteen pounds in weight during the preceding three weeks and the sputum was positive. The larynx showed small granulations posteriorly over one-third of the true cords. Diagnosis was tuberculosis of the larynx. Patient was put on bed-rest. Temperature stayed elevated to 100°F. for first two weeks but since then was more nearly normal.

After two and a half months he was transferred to another city hospital where he stayed for two months and then to a hospital outside of New York where he resided for five and a half months prior to transfer to Presbyterian Hospital. At the last hospital prior to transfer to Presbyterian Hospital the patient showed no significant changes in his condition. The report of the X-ray examination on admission is as follows: "There is an end stage caseous pneumonic tuberculosis involving the left upper lobe with marked thickening of the overlying pleura and retraction of the trachea towards this side. Areas of increased illumination are present in the infraclavicular region. Acinous-nodose infiltration in the left mid-lung field. Adhesions to the left leaf of the diaphragm. Exudative-productive infiltration in the upper one-half of the right lung with an occasional nodular infiltration in the right base. The heart is shifted toward the left. The left mastoid shows no pneumatization with productive changes in the periantral and posterior canal wall region. In the antrum area there is an increased density which may be due to erosion or the presence of a small choleostoma. No destructive changes. The right mastoid shows incomplete pneumatization." X-ray examination at discharge showed no change from the admission film. During the period of five and one-half months the patient was at rest in bed most of the time but was allowed bathroom privileges and was allowed up for meals. The temperature ranged from 98° to 99°F. and occasionally to 99.6°F. The admission weight was 131 lbs. and on discharge 136 lbs. Sedimentation rate was 63 mm. in 45 minutes. Sputum was positive, Gaffky IV.

Physical examination showed a fairly well developed and nourished Russian male, forty-two years of age. Over the right apex, dulness and diminished breath sounds of a bronchovesicular character were heard. There were a few medium moist râles. The left lung showed an area of cracked-pot sound, between the second and third ribs and in the mid-clavicular line. On auscultation amphoric breathing with many medium moist râles were heard.

Haemoglobin 105 per cent; red cells 5,500,000; white cells 14,000; polynuclears 70 per cent. Sputum was positive for tubercule bacilli.

The patient's temperature during the first four days at Presbyterian Hospital ranged between 99° and 99.6°F. He was then put in the equalizing pressure chamber with an equalizing pressure between 5 and 5.5 cm., for the first week, seven and a half hours a day, and from then on thirteen hours a day. He was treated for the most part seven days a week, the duration of treatment on Sundays being reduced to eight hours. This treatment was carried on in the alternating pressure chamber, utilizing the inner box for equalizing pressure. After an interval of one month, during the installation of the transportable chamber, the patient was treated in the latter apparatus for a period of three weeks. One week later he was returned to the city hospital.

During the first three months of treatment his weight gradually increased from 133 to 154 pounds. The sedimentation rate gradually decreased from 56 mm. to 6 mm. in an hour. (See chart 7.) His temperature range assumed a lower level, from 97° to 98.6°F. for the most part. His cough diminished and the sputum decreased from about 50 cc. to 4 cc. daily. The sputum was positive.

On discharge, at the end of three and three-quarter months' treatment, the lungs showed, on the right side, slight dulness at the apex, without râles; on the left side, the breath sounds were bronchovesicular from the second to the third interspace with few medium moist râles after coughing. Dulness was present over the left anterior chest from the second to the fourth interspace. Examination of the larynx at this time showed normal appearing vocal cords. According to the laryngologists there was no evidence of a tuberculous process in the larynx.

Two months after equalizing pressure had begun, the roentgenological report noted some clearing in both upper lung fields. After four months of treatment, the roentgenological report noted definite regression of the pulmonary infiltration in both upper lung fields, more marked in the left lung. (See figures 18, 19, 20 and 21.) Planigraphic films were taken during the course of treatment. These had shown several cavities in the left lung field near the hilum and in the upper lobe. It could not be determined that any change had taken place in the size of these cavities. It is possible that three small areas of translucency in the upper left lung field near the periphery disappeared during the course of the treatment, although the subsequent plani-

BODY WEIGHT
170
160
150
140
130

graphic films were not strictly comparable to those taken at the onset of the disease. The accompanying X-ray films vary somewhat in exposure, the last one (Number 21) being slightly overexposed.

Comment: This patient was known to have had tuberculosis with a cavity in the left lung for ten years. Equalizing pressure therapy was

SEDIMENTATION RATE AND BODY WEIGHT OF A PATIENT DURING RESIDENCE IN EQUALIZING PRESSURE CHAMBER.

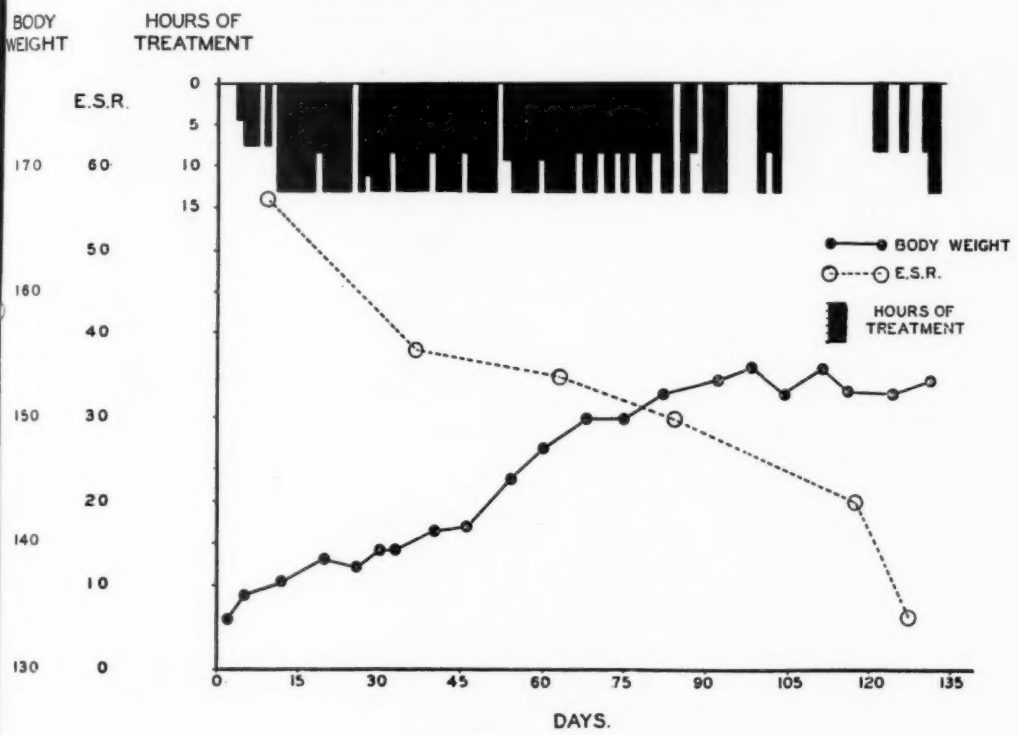
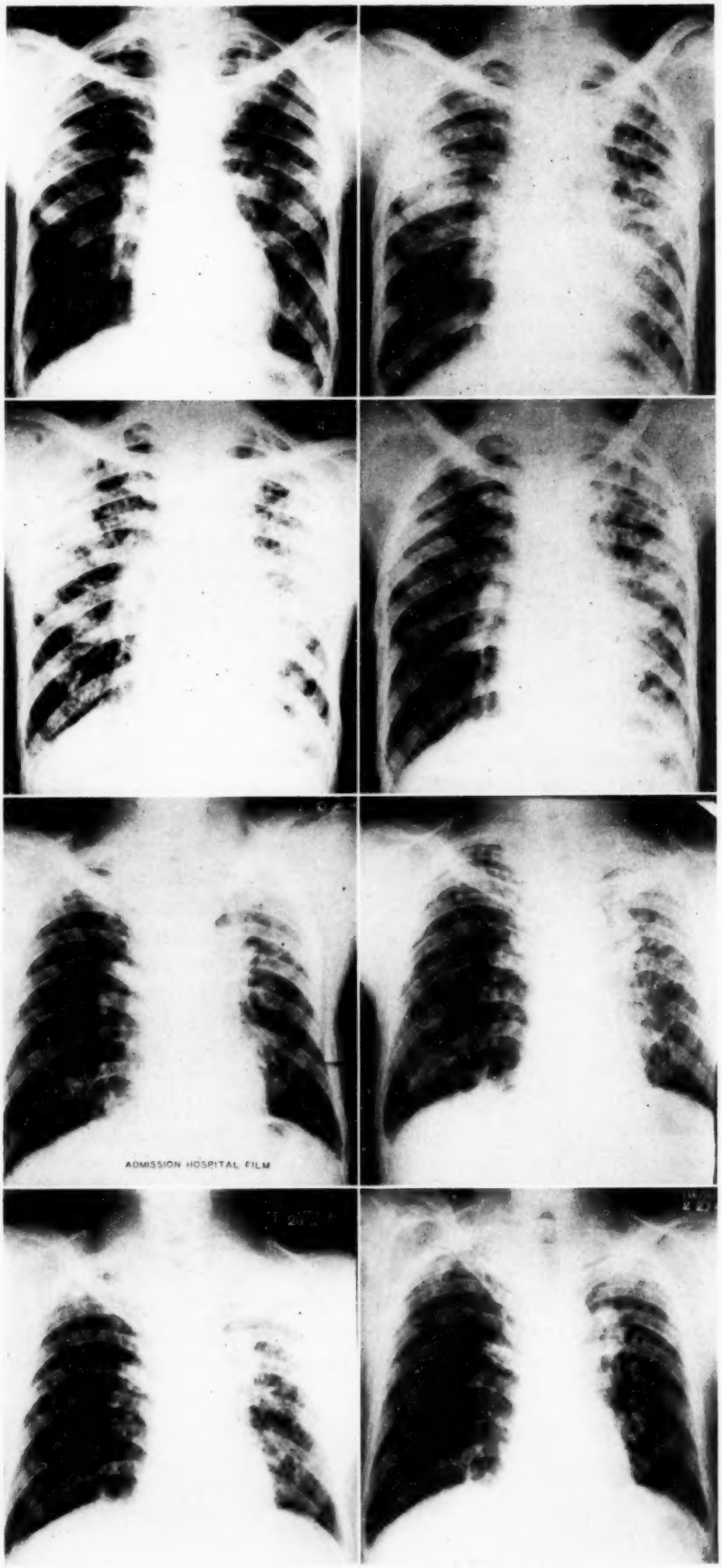


CHART 7

employed to investigate the possible effects of this type of lung rest in a case of long duration. Although no definite change in the cavities was apparently produced, the patient was clinically much better. His cough which had previously been frequent and hacking, with attacks of paroxysmal coughing, almost disappeared. The sputum decreased from 50 to 4 cc. daily. The sedimentation rate became normal and he gained



FIGS. 14–21

weight for the first time in ten years. After he had gained twenty pounds during the first three months, his weight remained stationary. X-ray examination showed definite regression of the lesions in both upper lung fields. The residual process on the right side was extremely slight and on physical examination no râles could be heard. On the left side there was a marked decrease in the number of râles and a change in the quality of the breath sounds from amphoric to bronchovesicular. He was returned to the city hospital, to determine whether further improvement would take place. No sign of tuberculosis of the larynx was present at the conclusion of treatment. The sputum was negative on discharge. During the following two months at a municipal tuberculosis institution, the sputum continued to be found negative on single, concentrated and gastric lavage specimens. The last report states that "recent X-ray examination does not reveal the presence of any cavitary lesion on either side but there are suspicious highlights present. There has been a decrease in the amount of infiltration since readmission to this institution with evidence of increasing fibrosis."

The arterial oxygen saturation and carbon dioxide content of the five patients treated by equalizing pressure are shown in table 1. A slight arterial anoxaemia was found on the initial observation in case 3 and a moderate anoxaemia in case 4. When the patient was exposed to alternating pressure alone the arterial oxygen saturation either fell slightly, as in case 1, or remained stationary, as in case 2. The carbon dioxide content was slightly lower in case 1 and slightly higher in case 2. In the latter patient the pH showed no significant change. In case 3, after two hours in equalizing pressure the arterial oxygen saturation rose from 94.9 to 100 per cent with a fall in carbon dioxide from 52.0 to 48.5 volumes per cent on one occasion and to 44.9 on another. These results are in harmony with the findings in animals previously reported, in which

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FIG. 14. (Upper left) Case 4. Admission film at city hospital.

FIG. 15. (Upper right) Case 4. After eleven weeks' bed-rest.

FIG. 16. (Second row left) Case 4. After fourteen weeks' bed-rest, at start of equalizing pressure treatment.

FIG. 17. (Second row right) Case 4. After four and one-half weeks of equalizing pressure treatment.

FIG. 18. (Third row left) Case 5. Before equalizing pressure.

FIG. 19. (Third row right) Case 5. After one week of equalizing pressure.

FIG. 20. (Lower left) Case 5. After three months' equalizing pressure.

FIG. 21. (Lower right) Case 5. After three and one-half months' equalizing pressure and five weeks' bed-rest.

it was shown that equalizing pressure increases the arterial oxygen saturation and lowers the carbon dioxide content in the arterial blood more efficiently than alternating pressure alone. It must be borne in mind that a state of hyperventilation might conceivably be produced by increasing unduly the pressure or the frequency of the cycle.

DISCUSSION

The procedure was found to be feasible in all five patients in whom it was tried. The first patient, after failure of pneumothorax subsequent to the treatment, wished to return. The third patient was glad to come back for a second course of therapy, in the attempt to close a residual cavity. Despite intermittent boredom with the routine, the coöperation which these ward patients gave was an indication of the practicability of the method.

Close observation and moving pictures in each instance revealed that little or no chest movement took place. On some occasions very slight alterations in the surface of the chest were detected but in the majority of times in which inspection took place without clothing no definite excursion of the chest wall was seen. If lung movements occurred they were obviously of minimal magnitude, compared to the conspicuous changes in pulmonary volume produced by ordinary respiration. As far as could be discerned by the fluoroscopic and roentgenographic examinations carried out during equalizing pressure (6), there was no movement of the diaphragm and costal margins evident under these circumstances, whereas during normal breathing the diaphragmatic excursion was conspicuous.

The results in the individual cases will be discussed in the order in which the patients came under observation. The first patient, as has been mentioned, was treated for two months, with only 4 cm. equalizing pressure and for about six hours a day. He was a man who had been getting unmistakably worse on bed-rest continuously for seven months. The change in his clinical condition was arrest of the previously observed downhill course and clinical betterment. Although the large cavities noted on the films did not change, the decrease in symptoms, cough, sputum and fever, was accompanied by objective evidences of improvement, such as clearing of shadows on X-ray films which had suggested inflammatory exudate, decrease in sedimentation rate and gain in weight. The changes were not as striking as those noticed on subsequent patients but they appeared quite encouraging at the time. Subsequent attempts

to close the cavities, first on one side and then on the other were unsuccessful. The patient was in a municipal tuberculosis institution in fair condition for fourteen months. He was discharged to the outpatient department, where lesions extended and prognosis was considered poor.

The second patient had advanced bilateral disease with smaller cavities on both sides; his course had been stationary on previous bed-rest, with maintained fever, cough and sputum. The initiation of a decided recovery process was unmistakable in this patient. Symptomatic improvement was striking: gain in weight, drop in sedimentation rate, marked diminution of cough and sputum and a normal temperature. The clearing of shadows in the X-ray films was marked. After transfer to a city hospital and subsequently to a convalescent sanitarium, the signs in the lungs cleared except for a few râles at the bases. The shadows in the X-ray films showed striking resolution, except for central foci and linear fibrosis. His sputum has been negative for over a year, and he is engaged in ambulatory work in the hospital, taking car of patients in the equalizing chamber. Apparent tuberculosis of the larynx disappeared at the conclusion of equalizing pressure treatment.

The third patient was also one of bilateral advanced disease, with larger cavities in both lungs. On previous bed-rest there was observed a slight improvement in the X-ray shadows, noted as "questionable" in the summary from the city hospital. Fever and cough, however, had continued and there had been no weight gain. In this patient, as in the former one, the signs of clinical improvement were unmistakable, such as normal temperature, gain in weight, marked decrease in cough and sputum, lowering of sedimentation rate and definite clearing of some of the lesions on both sides according to X-ray examination. Further rest at a city hospital and a sanitarium resulted in a continuation of the weight gain, and further resolution of the nodular shadows according to X-ray. He was readmitted for equalizing pressure because of progressive enlargement of the single cavity in the left upper lobe. The other cavities in the left lung and two cavities in the right lung, together with considerable nodular and dense areas of infiltration in each lung, had cleared. There remained the single cavity referred to in the periphery of the upper left lung field, and fine nodular shadows still present in each lung.

This cavity in the left lung field, which had increased on bed-rest five months previous was carefully studied by planigraphic films as

well as stereoscopic films. At the end of one month, the depth of the cavity had contracted to one-half its size; at two months, the width of the cavity was decreased one-half and the wall of the cavity, formerly thick and easily seen, was difficult to make out. The nodular shadows were decreased in both lungs. At the end of two and a half months, the total dimensions of the cavity had decreased one-fourth. The walls of the cavity were just discernible. He had gained weight. Sedimentation time was normal from the outset. The râles in both lungs were definitely diminished.

The fourth patient showed the signs of terminal illness. He was a Negro who at rest in bed in a city hospital had developed an extraordinary extension of the disease to both sides with increasing cavity. The fever was high on admission. He was dyspnoeic at rest, weak, toxaemic, coughing frequently and abundantly. He was admitted for treatment in equalizing pressure with the idea of observing the effect of lung rest on the clinical course of this type of swiftly advancing tuberculosis. There were some definite evidences of improvement, such as a lower temperature curve, increased strength, clearing of shadows representing inflammatory exudate in the right lung field. The sedimentation rate continued to be elevated and the downward course of weight loss continued. Following a tuberculous pneumonia (or the signs of sudden extension of a massive, dense process according to X-ray) he was removed to an oxygen room for three weeks. Later the lungs showed increasing excavation. The effect of sulfapyridine was interesting in that on two occasions it kept the temperature normal for a period of from eight to ten days, possibly as an effect on secondary invading organisms. After a period at home, he became suddenly worse and died later at a city hospital. The limitations of local rest therapy are clearly revealed in this case. In the presence of a rapid downhill course in a Negro with little or no resistance, only temporary clinical improvement was observed to an extent much less than that seen in the two previous cases.

The fifth patient was also selected to determine the possible range of effectiveness of the method. A man with tuberculosis and known cavity for ten years was selected. Although the cavity did not apparently change appreciably in size, the clearing of old shadows of inflammatory exudate seemed definite. The lung signs improved and the patient gained weight for the first time in ten years. Although he did not have definite fever before admission, the range of temperature was almost a degree lower on discharge. The sedimentation rate became normal.

Cough and sputum diminished strikingly. It seemed doubtful that he had an active lesion on the right side on discharge. The sputum became negative and stayed negative during the following two months, with continued clearing of mottled lung shadows. This patient as well as the second one showed a clearing of all laryngeal involvement, previously diagnosed as tuberculous laryngitis.

Omitting the temporary improvement that occurred in the clinical state of the Negro with rapidly advancing tuberculosis, the other four patients showed a consistent response to inauguration of local lung rest: (*1*) unusually marked gain in weight; (*2*) fall in sedimentation rate and temperature to normal; (*3*) decrease in symptoms such as cough, sputum, malaise; (*4*) unmistakable clearing of X-ray shadows, including cavity, with persistence or extension of improvement subsequently in all but the first patient in whom pneumothorax was attempted on each side without success.

That the transfer to an endowed hospital with presumably better food and more rigid body rest might have been factors in the improvement observed may be thought of. However, such improvement was not once observed in 8 similar cases taken from the same city hospital, treated with the same diet and complete bed-rest in either a filtered air chamber (9) or an oxygen chamber (10). It is freely acknowledged that these previous cases were not matched with the present series or intended as controls.

Except for the absence of vitamins, the diet was the same as in the present series. They resided continuously in specially constructed chambers, and were at rest in bed continuously during the entire period. The treatment with either 50 per cent oxygen or filtered air did not, however, modify the expected course of the disease, as seemed to occur in the present series. Although the number of cases is small, every attempt was made to select patients in whom a spontaneous resolution of the disease was considered very unlikely both by the author as well as the consulting staff of the city hospital from which they were transferred.

If the tentative conclusion that the process of resolution in pulmonary tuberculosis is aided by equalizing pressure therapy, the mechanism by which this is accomplished may be inquired into. In the first appraisal of the theoretical value of this procedure it was stated that local lung rest might facilitate the healing process. This was inferred from reported opinion that strict body rest is the most effective remedy for active tuberculosis. Mention might also be made that cessation of voluntary

respiration takes place at the end of a normal expiration, namely, at the time when the negative intrapleural pressure is least. Pinner (4) has expressed the view that a relaxation of the lung and consequently a decrease in the elastic tension of the lung favors the mechanism of healing. During residence, therefore, in the equalizing pressure chamber the elastic tension of lung tissue is continuously at a relatively low level, and there is not the rhythmical increase in tension which the act of inspiration induces. Amberson (1b) has mentioned that caseous areas are apt to heal by fibrous encapsulation, that this process is encouraged by diminished diffusion of toxins from the tuberculous lesion, and that decrease of lung movement lessens the diffusion of these toxins. Cessation of lung movement and local lung rest would, therefore, facilitate encapsulation of caseous areas by fibrous tissue. It should also be emphasized that the patients treated in this series had a special type of body rest. It appeared that a state of relaxation took place in which for hours at a time the patients showed not only absence of chest movement but absence of movement of the skeletal musculature.

SUMMARY AND CONCLUSIONS

Five patients with advanced bilateral pulmonary tuberculosis, who were considered unsuitable for any type of collapse therapy, were treated by a method of local lung rest which provided adequate pulmonary ventilation without lung movement; this was done after a previous control period of bed-rest. By equalizing the pressures on the inner and outer side of the chest wall, as well as on the upper and lower surface of the diaphragm, it was possible to pass air in and out of the lungs without discernible movement of the costal margins or the diaphragm.

Four patients showed a consistent response to equalizing pressure therapy for a period of two to four months, namely, (*1*) marked decrease in cough and sputum, (*2*) fall in sedimentation rate and temperature to normal, (*3*) definite clearing of shadows in X-ray films, including cavities, (*4*) subjective recognition of improvement in terms of well-being and loss of malaise. In the first, partially treated patient these signs of improvement were less marked; the large walled-off cavities persisted and subsequent attempts to collapse them, first on one side, then on the other, were unsuccessful.

In the second patient, resolution of an extensive tuberculous process, characterized by honeycombing in both lungs, took place following equalizing pressure therapy, with the development and persistence of a negative sputum for a period now over one year. He is now engaged in

part-time work which requires mild physical activity. In the third patient, unmistakable progressive improvement followed the first course of equalizing pressure therapy, with clearing of dense inflammatory exudate and cavities of considerable size in both lungs. However, five months after treatment a small residual cavity in the left upper lobe enlarged and during the following five months of bed-rest was more than double its former size, that is, five months after the equalizing pressure treatment. A second course of equalizing pressure resulted in an abrupt shrinking of the cavity which continued to the present time.

In the fourth patient, a Negro with rapidly advancing tuberculosis and high intermittent fever, clinical improvement manifested itself during the first month of equalizing pressure treatment, including decided retrogression of lesions in the right lung according to X-ray films. A subsequent tuberculous pneumonia resulted in extension of the disease and ultimate death. In the fifth patient, a man with a known tuberculous cavity for ten years, clinical and roentgenological improvement was observed, with the development of negative sputum and gastric lavage for a period now two months after discharge.

The weight gain seems mainly attributable to the lack of work on the part of the respiratory musculature, and the special body rest and relaxation which cessation of voluntary respiration and residence in the equalizing chamber engendered.

The response of these patients to equalizing pressure therapy suggests that immobilization of the lung, with complete body rest in addition, aids the process of resolution in pulmonary tuberculosis.

Since immobilizing the lung helped to bring about a stabilization of the disease and to initiate a recovery process in patients with advanced tuberculosis previously unresponsive to bed-rest, the method may be justifiably tried in less severe cases. It should be understood that subsequent treatment must still utilize the measures known to be of value in pulmonary tuberculosis. These might include additional rest and graduated activity; in some cases collapse measures might be necessary to secure a durable arrest of the disease.

The author wishes to express his sincere appreciation to Dr. J. Burns Amberson, Jr., for his valuable help during the conduct of this investigation, including the selection of cases and the appraisal of the results obtained.

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ALTERNATING EQUALIZING PRESSURE CHAMBER AND CONTROL PRESSURE PANEL[1,2]

Its Technical Description and Operation

ALVAN L. BARACH

With the technical assistance of Morris Eckman

DESCRIPTION

The chamber is seven feet long, elliptical in section with axes 30 inches and 24 inches respectively. The ends are convex and roughly ellipsoid in shape. It is divided in three sections, the head section D, the body section A, and the cooling-coil section T. Sections A and D are separated by a removable dividing plate (C) which holds a sponge-rubber collar for the patient's neck. The sections A and D are connected by two ducts, running on the outside of the chamber shell, containing two valves (B). These valves are used for controlling the equalizing pressure differential.

The door (E) swings on a swivel type hinge and is tightened by eight screw handles. A one-half inch rubber gasket permits the door to make a gas tight seal both on positive and negative pressure.

The frame support is made of heavy channel steel and is mounted on four rubber tired ball-bearing casters of six inch diameter. The chamber rests on the frame support in a cradle mounted on rubber to damp vibration.

The driving mechanism rests on a heavy wood platform which is attached to the frame support by means of rubber mountings (U).

The motor (K) driving the compressor is a one and one-half H. P. alternating current motor. The compressor (J) is of the oil-less displacement type and has a 220 cu. ft./min. capacity. The rotary valve (G) is a four-way valve which reverses the compressor outlets four times to each revolution. The one-half H. P. motor of the reducing gear

[1] From the Department of Medicine, Columbia University, College of Physicians and Surgeons, and the Presbyterian Hospital, New York City.

[2] For complete bibliography see previous paper, published in Am. Rev. Tuberc.

assembly (F) rotates the rotary valve from ten to sixteen times per minute thus creating from twenty to thirty-two cycles of pressure depending on adjustment. An alternating pressure control valve (H) connects the suction side to the pressure side of the compressor. Opening this valve brings about a shunting of air outside of the chamber thus reducing the pressure. Two silencers (L) are set in the air circuit to silence air and compressor noises. One runs from the rotary valve to the outlet to room air at (O), the other from the opposite side of the rotary valve to the chamber inlet at (N). This latter silencer is attached to the chamber at (N) by means of a rubber expansion-joint for flexibility and reduction of vibration transmission.

On the underside of the chamber a drain (M) is attached for draining off condensed moisture. This drain opens automatically only during the positive part of the pressure cycle.

At the head end of the chamber shell, on the underside, there is a screw jack for elevating the chamber. It is controlled by the elevator handle (P).

The cooling coils are of three quarter inch copper tubing, and are placed in section T in staggered formation so that the air currents are broken up into small streams thus insuring efficient cooling and dehumidification. These coils may be attached to a cold water tap or a brine system.

OPERATION OF CHAMBER

Positive pressure: Air is drawn in from room through outlet O, passes through silencer L, then from the left opening through the top opening of rotary valve (G) into the suction opening at the top of the compressor (J). The air then passes from the pressure opening at the bottom of the compressor through the bottom opening of the rotary valve, then through the right opening of the rotary valve through the second silencer and enters the cooling section (T) of the chamber at N.

The air then proceeds over the cooling coils and enters the alternating pressure section D where the pressure is shown on alternating pressure gauge (R). From section D the air passes into section A through the ducts on the outside of the chamber shell. By turning valves (B) slightly the air is delayed in entering section A with the result that the pressure is lower in this section. The difference in pressure between sections A and D may be read on gauge (S). This entire operation takes place while the rotary valve is making one-quarter of a turn.

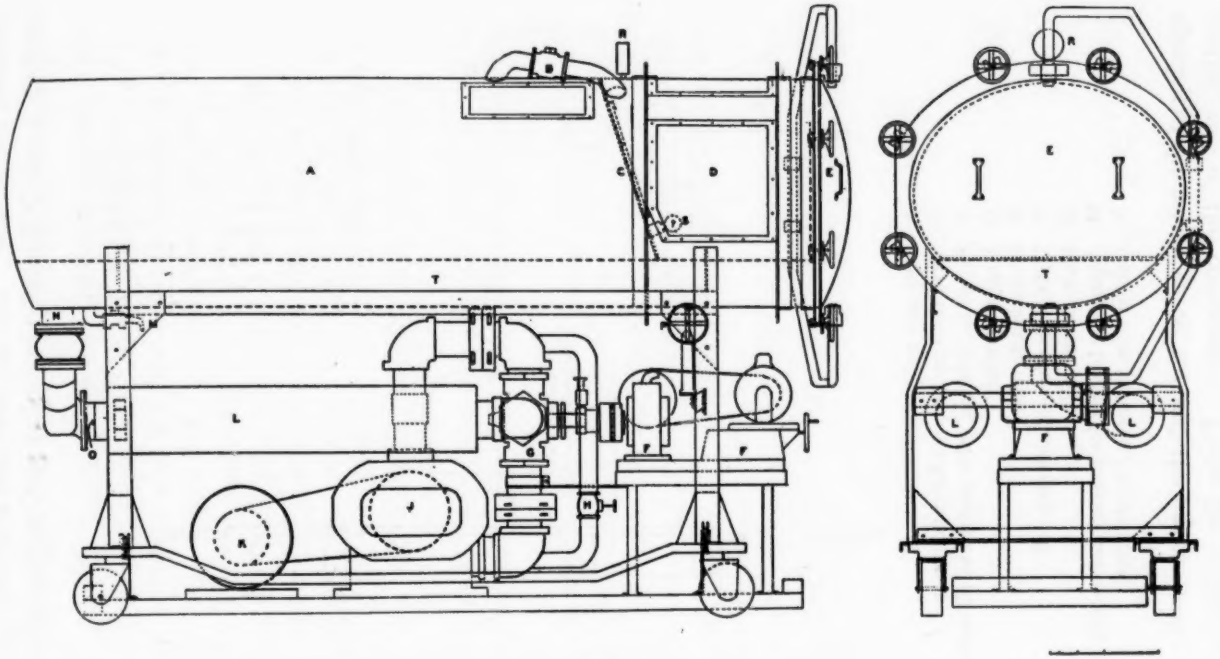


FIG. 1

A Equalizing pressure section (body section)
B Equalizing pressure control valve
C Dividing plate with collar
D Alternating pressure section (head section)
E Door
F Reducing gear assembly for rotary valve
G Four-way rotary valve
H Alternating pressure control valve
J Compressor
K Compressor motor
L Silencer
M Condensation drain
N Inlet to chamber
O Outlet to room air
P Elevator handle
R Alternating pressure gauge
S Equalizing pressure differential gauge
T Cooling coil section
U Rubber mounting

Negative pressure: During the next quarter turn the rotary valve has reversed the air flow. The air flow then is as follows: it is sucked from sections A and D through the cooling section, the right silencer, the right

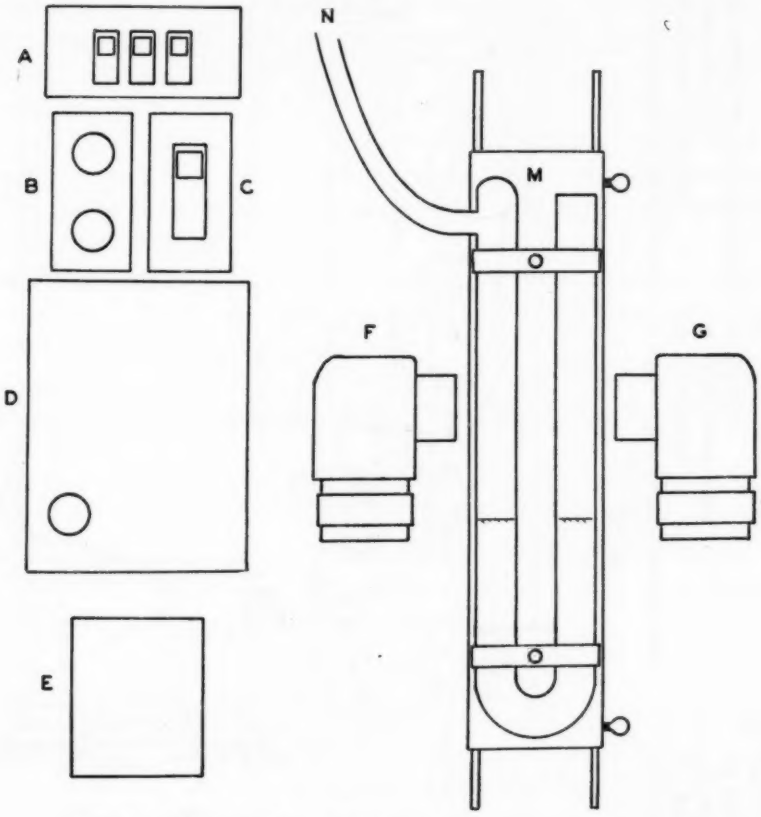


FIG. 2. A Light and radio switches
B Start and stop switches for compressor
C Switch for rotating valve motor and photoelectric cell
D Magnetic switch
E Photoelectric relay
F Light source for photoelectric cell
G Photoelectric cell
M Adjustable bracket for mercury manometer
N Rubber tube (connected to chamber)

opening of the rotary valve, through the top of the rotary valve into the suction end of the compressor. From the compressor the air passes through the bottom of the rotary valve, then through the left opening

of the rotary valve through the left silencer to the outside air. (See figure 1.)

CONTROL PANEL OF ALTERNATING EQUALIZING PRESSURE CHAMBER

The mercury manometer, mounted on an adjustable bracket (M) is attached to the chamber by means of a rubber tube (N). The arms of the manometer lie in a plane with the light source (F) and photo-cell (G) so that the light beam passes from the light source, through both arms of the manometer to the photo-cell.

The adjustable bracket is set at a point where the mercury in the manometer will not interrupt the light beam during normal operation of the machine. Should the pressure in the chamber rise too high or fall too low in any cycle of the machine, the mercury in the open arm or closed arm, as the case may be, will rise sufficiently to interrupt the light beam.

When the light beam is interrupted the photoelectric relay (E) is inactivated and cases the magnetic switch D to break the circuit shutting off the compressor.

Directions for starting and stopping: In starting the chamber the photo-electric and rotating-valve motor switch (C) is turned on. Allow twenty seconds time to elapse for the photo-cell to warm up. The compressor is then turned on by pressing the starting button (upper one) on the compressor switch (B). To stop the compressor press the stop button (lower one) of compressor switch B.

Should the compressor stop because of too high or too low a pressure in the chamber, it may be started again by first resetting the reset button on magnetic switch (D) and then pressing the starting button on compressor switch (B). (See figure 2.)

TUBERCULIN TESTING IN CHICAGO SCHOOLS[1]

Tuberculin Tests on 167,345 Children with X-ray Films of 27,401 Tuberculin Reactors

FREDERICK TICE

Case-finding with the adult as periphery and the contact as pivot, has long been the policy of the Municipal Tuberculosis Sanitarium, and our surveys have centered on such groups as lodging house residents, inmates of the County Jail and the Bridewell, the relief shelters and residents of the congested areas, approached through a house-to-house canvass. In line with the experience of Chadwick (1) and others, case-finding in children has been found by us to be expensive and comparatively unproductive. Nevertheless, in view of the allocation of funds from the Tuberculosis Institute of Chicago and Cook County and for certain other reasons, the survey was undertaken. The additional motivating influences, in order of importance, ran: (*1*) the anticipation of an appreciable amount of new tuberculosis in the high schools and in the follow-up of the tuberculin-positives; (*2*) utilization of the city-wide survey as a check on the existent case-finding machinery and as a measuring rod of city-wide morbidity; (*3*) educational values.

The tuberculin used: PPD, the Mantoux method and the single test was the procedure selected. While supposedly the ideal, the two test method, in large scale application, has very serious disadvantages. Aside from the extra expenditure and time involved, important considerations in a city-wide survey, the double test, in our experience, evoked some degree of opposition in children, parents and teachers. Some of the children were worried about the "second stick"; the parents were worried by the children's worries and the teachers objected to disruption of their routine.

Dosage selected for the survey: Regarding the amount of PPD to be used, it was felt that a dose somewhere between the first and second strength PPD would register sufficient accuracy for the purposes already mentioned, skirting, at the same time, the unpleasantness of the single large injection. Bearing in mind the high percentage of Negroes

[1] From the Municipal Tuberculosis Sanatorium, Chicago, Illinois.

in the total population, the fair percentage of Mexicans in certain districts, the injection had to be small enough to discount, in advance, an undue proportion of four-plus reactions, but large enough to uncover clinically important cases of tuberculosis, and to give us some idea as to the morbidity picture in the various districts.

To meet these conditions the procedure, as chosen and outlined by Dr. M. R. Lichtenstein, our allergist, was a single injection of one-tenth the usual final dose of PPD, an amount equivalent to 0.000,5 mg. PPD or approximately 0.1 cc. of a 1 to 1,150 solution of Old Tuberculin. For the general mass of the work this dose, one-tenth the second strength of PPD, was used until November, 1939. Using this strength, the percentage of reactors, in comparison with certain other large urban centres, seemed low.

In an effort to go a little deeper into the allergic status of the community as a whole, it was determined, subsequent to November, 1939, to double the amount of PPD, making the dose one-fifth instead of one-tenth final strength. This dosage, 0.001 mg. PPD in 0.1 cc., was similar to the amount used by Plunkett and Siegal (2) and corresponds roughly to 0.1 cc. of 1 to 575 Old Tuberculin (0.2 mg. OT).

X-Ray equipment and technique: Our X-ray problem hinged on the necessity of examining large numbers of children in a comparatively short time. The work had to be done in the schools. In view of the volume and certain innate deficiencies, portable X-ray equipment was considered unsatisfactory. The solution seemed to lie in some kind of a self-contained and completely mobile unit. With this objective in mind a unit was devised, the first of its kind, as far as we know, to be used. As developed and built the mobile unit consists of a completely equipped, shockproof, 100 milliampere X-ray machine with a rotary converter, automatic cassette changer, and all accessories, including three dressing rooms, dark room for loading cassettes, lead-lined cabinets for storage, four heaters and a ventilating fan. The equipment is mounted on a one and one-half ton, balloon-tired truck with a van body, 181 inch wheelbase, an inside length of 15 feet and width of 7 feet.

RESULTS AND TABULATIONS

The detailed results of the program will be available in a Bulletin to be published in the near future. Within the scope of this paper it is impossible to present more than a condensation of the results and a few of the tabulations. Arranged according to grades, of the 98,745 ele-

mentary school children examined, 14,143 were tested in kindergarten, 39,446 in first grade, 723 in second grade, 747 in third grade, 863 in fourth grade, 896 in fifth grade, 657 in sixth grade, 764 in seventh grade, 40,002 in eighth grade, and 504 ungraded. Of the 65,180 high school

TABLE 1

Summary of results by type of school

TYPE OF SCHOOL	NUMBER OF SCHOOLS	NUMBER PUPILS TESTED	POSITIVE	
			Number	Per cent
Public				
Elementary	561	74,334	9,529	12.82
High	115	57,211	12,209	21.34
Total	676	131,545	21,738	16.53
Catholic				
Elementary	301	21,774	2,697	12.39
High	47	7,969	1,670	20.96
Total	348	29,743	4,367	14.68
Lutheran				
Elementary	46	2,637	271	10.28
High	0	0	0	—
Total	46	2,637	271	10.28
Total				
Elementary	908	98,745	12,497	12.66
High	162	65,180	13,879	21.29
Total	1,070	163,925	26,376	16.09
Miscellaneous				
Colleges	3	405	137	33.83
Trade or vocational	10	1,207	393	32.56
Junior colleges	2	1,728	477	27.60
Academy (private high)	1	23	7	30.43
Girls home and school	1	57	11	19.30
Total	17	3,420	1,025	29.97
Grand total—All schools	1,087	167,345	27,401	16.37

pupils examined, 23,478 were tested in the freshman year, 19,013 in sophomore year, 11,982 in junior year, 10,591 in senior year, 116 ungraded.

Regarding percentage of positive reactors, table 1 gives the breakdown.

The explanation of the low percentage of reactors will become apparent

in later tables. For reasons too lengthy to be given here, only the kindergarten, first and eighth grades were tested routinely. The normally low incidence in the early grades operates against the eighth grade to pull the total percentage down. In comparing the Catholic, Lutheran and public schools, one notes in the tabulation slight variations in the reactor rates for both elementary and high schools and these variations may be due, perhaps, to underlying racial and sociological factors. Throughout the series the reactor rate, as was to be expected, varied directly with the grade and age.

Race: Since Chicago has a large Negro population (275,000 estimated), and since the Negro mortality is greatly out of proportion, 281.7 per 10,000 against 34.0 per 100,000 for the whites, it was considered essential to distribute the results according to race. Graph 1 gives the picture. For almost all age periods, the reactor rate ran twice as high and more for the Negroes.

The figures for the Mexican ran still higher than for the Negro. Taking all ages, including kindergarten and first grade, the reaction rate for the Negro was 27.34 per cent against 34.57 per cent for the Mexican.

Degree of reaction: In our series the proportion of four-plus reactions was higher than in many of the reports seen in the literature. Four-plus reactions were 8.08 per cent for the white, 20.69 per cent for the Negro, and 21.00 per cent for the Mexican. It is interesting to note that from the racial angle, incidence of reaction and quality or degree of reaction ran on closely parallel lines; roughly, in comparison with the white, reactions in the Negro were more than twice as numerous and more than twice as intensive.

Low reaction incidence in Chicago: In comparison with surveys elsewhere, with special reference to metropolitan surveys, the reaction rate in Chicago, on the basis of the figures given, was low. Discounting, for the moment, the question of procedure and dosage, there was another factor undoubtedly influencing this result.

The survey in Chicago was city-wide, including all schools, all economic levels, and the small number of reactors in the more prosperous districts diluted the total figures. Tuberculosis mortality in Chicago is largely a matter of what one might call economic geography. Four of the 75 census districts, with a population of 358,127, account for 38.0 per cent of all tuberculosis deaths. Elaborated against a map of the city, economic status, mortality and morbidity are closely allied. Very possibly, therefore, to economic geography may be ascribed, in part, the wide

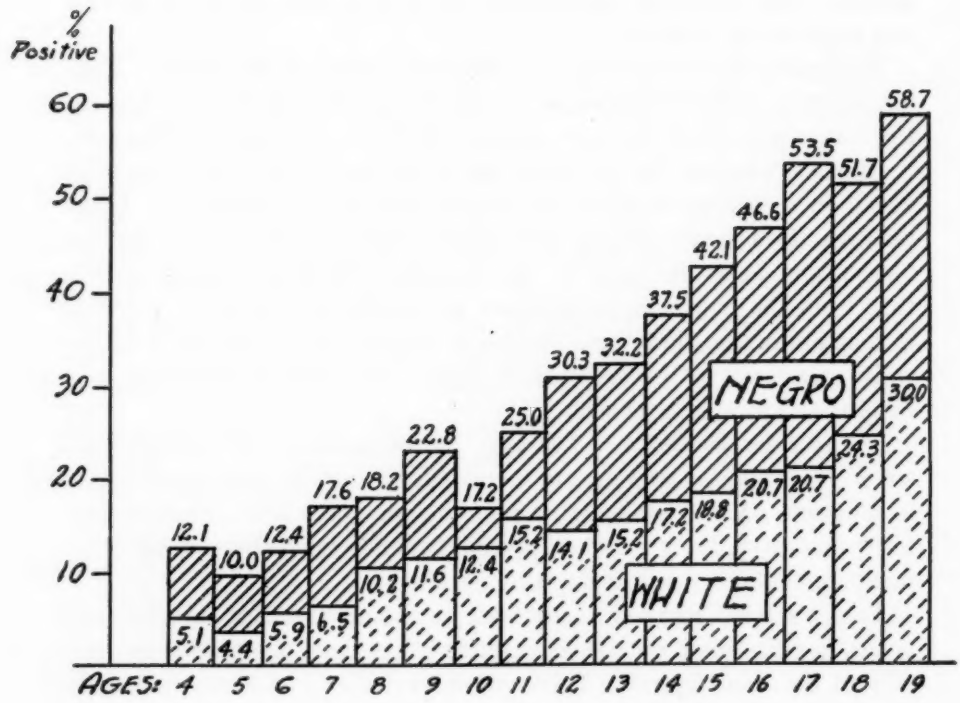
discrepancies in reaction rate reported for various cities. A survey confined largely, or entirely, to areas of high mortality will give an unduly high reaction rate and a correspondingly inaccurate picture of the infection index throughout the city as a whole.

GRAPH - I -

PERCENT POSITIVE

BY AGE & RACE

167,345 CHILDREN TESTED
27,401 POSITIVES



Mixed districts: In an effort to weigh the racial factor with an equalization of living conditions, 1,309 pupils were tested in a mixed school in a poor district. Five hundred of the pupils were white, 148 Negro and 661 Mexican. The rates, including kindergarten and first grade, ran

18.40 per cent for the white, 22.97 per cent for the Negro and 28.90 per cent for the Mexican.

The difference in the reactor incidence, already stressed, still prevails but the margin has narrowed. In the age period of the eighth grade the ratio is 1.25 for the Negro to 1.0 for the white, a much closer gap than the 2 to 1 figure for the study as a whole.

Controls: In 5,015 children examined in the same schools (same room, same time), 2,073 with the standard two-test PPD, 2,942 with our original one-test method (0.000,5 mg. PPD) the two-test method showed an advantage of 7.9 per cent.

A control of our second test procedure, the 0.001 mg. PPD (instituted November 14, 1939) against standard second-strength PPD, showed an advantage of 4.7 per cent in favor of the latter. In this control and in connection with the stronger dose on the negative reactors retested, an interesting situation developed, namely, fewer additional reactions in the Mexican than in the Negro, and fewer in the Negro than in the white. Whether this latter ratio, which runs contrary to the usual racial trend, has any epidemiological significance is a matter of speculation. One is inclined to think of an "early threshold of sensitivity and a fixed depth" in both the Mexican and the Negro.

This concept of "early threshold" seems borne out by the incidence of four-plus reactions as shown throughout the program, 21.00 per cent four-plus reactions in the Mexicans, 20.69 per cent in the Negroes and 8.08 per cent in the whites. The "fixed depth" seems indicated by the comparatively few additional reactions found in the Negro and Mexican on second tests with high dosage. The number of children involved was comparatively small, a total of 1,016, 258 whites, 662 Negroes, and 96 Mexicans. Whether this whole subject is bound up with the pathological picture and the genotypic differences discussed by Long (3), Pinner and Kasper (4) and others, is again an exercise in speculation. Whatever the explanation and whether on a racial basis or not, the irregularity of response to the second test interfered with the control as a measuring rod to test the adequacy of the single test and prohibited the use of the figure 4.72 per cent as a corrective for this inadequacy.

ACTUAL CASE-FINDING RESULTS

Altogether, in the 167,345 children and adolescents tested and through the 23,532 X-ray films taken, 218 cases of reinfection-type tuberculosis were found at the first examination, 107 more cases were found in the

follow-up of the suspects among the children, 226 cases were uncovered through the follow-up of the tuberculin reactors into the home and 35 cases among teachers and school personnel. In all, then, 586 cases of reinfection-type tuberculosis, hitherto unknown, were brought to the register. Table 2 furnishes detail on the cases discovered at the first examination.

In considering the incidence of reinfection-type tuberculosis as represented in the table (0.92 per cent of those X-rayed) it is necessary

TABLE 2

Tuberculosis found according to type of disease and type of school

(Percentages Based on Total Children X-rayed)

X-RAY DIAGNOSIS	TOTAL ALL SCHOOLS		TOTAL ELEMENTARY		TOTAL HIGH SCHOOLS		TOTAL MISCELLANEOUS SCHOOLS	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Adult type								
Minimal	109	0.4	34	0.3	68	0.5	7	0.8
Moderately advanced	94	0.4	36	0.3	55	0.4	3	0.3
Far advanced	15	0.1	5	0.1	10	0.1	0	—
Total	218	0.9	75	0.7	133	1.0	10	1.1
*Primary Type**								
Tracheobronchial	2,324	9.9	1,297	12.8	990	7.9	37	4.1
Parenchymal	5	0.0	4	0.0	1	0.0	0	—
Combined	2,034	8.6	865	8.6	1,105	8.9	64	7.0
Tracheobronchial and suspected adult type	109	0.5	54	0.5	53	0.4	2	0.2
Combined and suspected adult type	52	0.2	21	0.2	30	0.2	1	0.1
	4,524	19.2	2,241	22.1	2,179	17.4	104	11.4

* "Primary type" includes both active and inactive disease.

to remember that the incidence is taken against the children X-rayed, not the children tested. If, for instance, the reinfection-type tuberculosis found in kindergarten and first grade were figured on the basis of the 53,589 children tested, the percentage of cases found would have been 0.015 per cent instead of 0.34 per cent. In the eighth grade, in the 40,002 children tested, the percentage of adult-type tuberculosis found would have been 0.15 per cent instead of 0.88 per cent. In high schools,

of 65,180 children tested, the percentage of adult or reinfection-type tuberculosis found would have been 0.20 per cent instead of 1.06 per cent.

Regarding incidence of serious tuberculosis in the grades, one moderately advanced case was found in the kindergarten, 4 moderately advanced cases in the first grade, 2 moderately advanced and one far

TABLE 3

Diagnosis according to race, sex and age groups

AGES	X-RAYED		REINFECTION TYPE				PRIMARY TYPE			
			White		Negro		White		Negro	
	White, number	Negro, number	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
4 to 7 years										
Male	745	320	0	—	4	1.2	165	22.2	75	23.4
Female	744	329	3	0.4	1	0.3	164	22.0	77	23.4
Total	1,489	649	3	0.2	5	0.8	329	22.1	152	23.4
8 to 11 years										
Male	188	43	0	—	0	—	36	19.1	6	13.9
Female	183	49	0	—	0	—	45	24.6	12	24.5
Total	371	92	0	—	0	—	81	21.8	18	19.6
12 to 15 years										
Male	4,869	1,013	25	0.5	8	0.8	1,015	20.8	206	20.3
Female	5,112	1,599	52	1.0	23	1.4	1,058	20.7	300	18.8
Total	9,981	2,612	77	0.8	31	1.2	2,073	20.8	506	19.4
16 years and over										
Male	3,413	845	30	0.9	6	0.7	559	16.4	127	15.0
Female	2,734	986	45	1.6	15	1.5	461	16.9	156	15.8
Total	6,147	1,831	75	1.2	21	1.2	1,020	16.6	283	15.4
Totals										
Male	9,215	2,221	55	0.6	18	0.8	1,775	19.3	414	18.6
Female	8,773	2,963	100	1.1	39	1.3	1,728	19.7	545	18.4
Total	17,988	5,184	155	0.9	57	1.1	3,503	19.5	959	18.5

advanced case in the intermediate grades, 27 moderately advanced and 4 far advanced cases in the eighth grade, and 55 moderately advanced and 10 far advanced cases in the high schools.

Race and sex: Taking the reactors of both races, the ratio of actual pulmonary disease to cases X-rayed is slightly higher in the Negro, an excess, to be exact, of 0.2 per cent. Regarding sex, analysis of the adoles-

cent groups merely emphasizes differences in incidence already well established. Table 3 shows the details according to race and sex.

FOLLOW-UP OBSERVATIONS

Aside from the question of insufficient personnel, the follow-up in a city-wide tuberculin testing program presents certain obvious difficulties. Total coöperation in a program of this kind is a vain illusion.

In a measure, the educationalist promoting a widespread tuberculin-testing campaign works against himself. During the preliminary educational stage and during the actual testing, in order to allay parental fears and invite coöperation, he must publicize the distinction between infection and disease and stress the fact that, in the great majority of instances, the positive test is not of serious import. Later on, as the follow-up develops, this publicity comes back to him as a boomerang. "The pamphlet says so and so." "The positive test is not serious. Why should I have my family X-rayed?"

Still another factor that hinders efficiency in the follow-up centres on a debatable question in immunity. Whom should we follow, the positive or the negative tuberculin reactors? In a highly infected milieu, is a robust reaction an asset or a liability? If we are at all favorably inclined toward immunizing procedures, such as BCG, we should logically regard the positive reaction as an asset, the negative reaction as a liability. The usual routine, of course, is to follow the reactors, and those who advocate the procedure affirm the higher percentage of tuberculosis in the reactors. It must be remembered, however, that this higher percentage may depend, to a large extent, on certain intrinsic errors: (*1*) the presence of slight, undetected tuberculosis in the reactors at the time of first examination; (*2*) continued contact of the reactors with open tuberculosis. Both factors, contact to infectious disease and already existent early tuberculosis in reactors, would materially influence the relative disease rate as between positive and negative reactors. Leaving infancy and the very early years aside, and eliminating the two possible sources of danger mentioned, family exposure and existent tuberculosis, it is open to question as to whether, in densely populated agreas, it is worth while to follow up the tuberculin-positive child.

All this, of course, does not apply to children diagnosed as suspects on the first X-ray film. In this group an appreciable amount of tuberculosis may be expected, and the follow-up is worth the effort and ex-

penditure. Over the three-year period, such a follow-up in the present survey disclosed 107 new cases of tuberculosis, 63 minimal, 29 moderately advanced and 15 far advanced. Two of the cases have died at the date of this report.

Prolonged observation of large numbers of children presents certain serious difficulties. Both as regards sudden advances, from suspicion to diagnosis, and as regards progress in recognized lesions, mass follow-up during the school age periods is disheartening. The unpredictable character of adult-type lesions in children and adolescents has been emphasized by Chadwick (5), Hetherington *et al.* (6), Novak and Kruglich (7) and others. The lack of a pointer, a prognostic finger, is something that must be faced, a handicap that seriously militates against the efficacy of the follow-up. How can we narrow the follow-up, contract the search from the many, showing similar X-ray evidence to the few actually threatened? Anything in the nature of an answer to this question will help solve the problem and give some meaning to mass follow-up work.

CASE FINDING THROUGH FOLLOW-UP OF THE REACTORS INTO THE HOME

We had hoped that the tuberculin-positive children, particularly in kindergarten and first grade, would lead the way to a fair volume of undiscovered tuberculosis in the contacts. To the surprise of the staff, in the overwhelming majority of instances where tuberculosis existed or had existed in the home, the follow-up to identify the source of infection was unnecessary. The case had already been located. Altogether, in 3,284 instances the source of infection was unmistakably established, and in only 226 cases was new tuberculosis found. Of the remaining 3,058, 1,380 were old pulmonary cases already registered and still living, some of them in institutions, many of them had received collapse therapy and turned negative, others were arrested at the date of the last examination. The remaining 1,678 established sources of infection were pulmonary deaths in cases registered with the clinics prior to death.

The comparatively small number of new cases found in the families of the positive reactors was both a disappointment and a satisfaction. We had anticipated a larger proportion of new tuberculosis and failure in this objective constituted disappointment. Regarding the satisfaction, it was encouraging to know that the existent case-finding machinery was effective, as shown by the fact that in 90 per cent of the cases the source of infection was already under supervision.

COST ANALYSIS AND A SUBSTITUTE FOR THE TUBERCULIN SCREEN

Over the three-year period the sum of $40,000.00 was allocated by The Tuberculosis Institute of Chicago and Cook County. This sum represents only a fraction of the expense and was used to pay for additional personnel and for some of the X-ray films. Much of the work was done by our own staff and practically all the clerical work by a carefully supervised WPA project. To gain a true cost figure it would be necessary to take all these factors into consideration and apply total personnel hours against payroll. Working along these lines, in an admittedly difficult task, due to interdigitation of activities, O'Neil and Bollman, our auditor and chief clerk, respectively, estimated the cost of the survey at $450.00 per case found.

This is expensive case-finding. Is it worth while? The matter resolves itself into a question of simple economics. Why work a low grade ore when rich ore is available and easily accessible to the case-finding machinery? Very recently case-finding machinery has been much improved and one specific improvement seems destined to revolutionize tuberculosis work. I refer to the miniature X-ray film and the mobile X-ray unit. A truck, furnished with such apparatus, equipped with cable to plug into the power sockets, can go from block to block and bring the X-ray directly to the doorstep. Total X-ray survey in areas of high tuberculosis mortality has long been the objective of public health men and the miniature, at last, brings this objective definitely within reach.

Using the miniature and the mobile unit, supplementing the publicity drive with house-to-house canvass by the field nurses, such a "total survey" is at present in full progress in the congested areas of Chicago's south side. In the two months of operation, ten thousand persons were X-rayed and 331 new cases of tuberculosis found on the first film. A comparison of this figure with the 218 cases so found among the 167,345 school children tested in the three years, establishes the relative merits of the two systems. Such results, doubtless soon to be confirmed by others, point to the miniature film as the case-finding instrument *par excellence*.

SUMMARY AND CONCLUSIONS

Over a three year period, 167,345 children were tested, of whom 27,401 were tuberculin-positive. In all, including the school children and the

cases found in the follow-up, 586 new cases were found at an estimated cost of $450.00 per case.

In view of the effort and expenditure and in the face of recent developments, case-finding limited to the school age groups is unproductive and economically contraindicated in large scale work.

Total X-ray survey, including examination of men, women and children in areas of excessive tuberculosis mortality, would seem to be the procedure of the future.

Though the tuberculin X-ray screen still has its place, according to present indications, the miniature X-ray film has stepped up to first place as a case-finding instrument.

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THE MINIATURE X-RAY FILM OF THE CHEST[1]

BRUCE H. DOUGLAS AND CARL C. BIRKELO

The surveying of certain groups for the detection of early tuberculosis has been recognized for sometime as a basic procedure in the program for the control of this communicable disease. Various methods have been devised for making surveys and all of them, whether using tuberculin testing as a preliminary screen or employing some form of X-ray examination directly, rely in the end on the roentgenological examination of the chest for the detection of the significant lesion.

The expense connected with making a satisfactory X-ray examination, however, has sharply limited the amount of work that could be done in this field. To a large extent cost has been responsible for the development of the practice of using the tuberculin test as a screen to detect from the many, those who have been infected, as evidenced by a positive test, for the final more expensive examination by X-ray.

While tuberculin testing has its place as a diagnostic aid, there are certain disadvantages to its use as a screening device for case-finding, such as the inconvenience of the repeated visits necessary, interpreting the reaction and repeating it on negatives if a two-dose method is employed.

One visit for an x-ray examination will suffice to procure a permanent record if there is a roentgenogram made at the first visit. In general it is easier to persuade people to have an X-ray examination than to have a skin test.

These considerations as well as others have led to a search for accurate yet inexpensive ways of making the X-ray examination of the chest for survey purposes. Recognizing that the well taken, full-size film is the most accurate method it has been felt that a close approach to this accuracy, if it could be had in a much less expensive method, would be more valuable as a case-finding procedure, since it could be more widely used.

Sensitized paper has been used for this purpose quite successfully at

[1] Presented at a session of the Medical Section at the 35th annual meeting of the American Trudeau Society, Cleveland, Ohio, June 4, 1940.

about one-half the cost of full-size celluloid film and almost as great accuracy.

The fluoroscope in the hands of some has been found economical, however, it is not as accurate and there is no permanent record made. Fellows (1) reports a 13 per cent error when compared with full-size film.

For sometime there have been numerous attempts to photograph the image on the fluorescent screen upon small films, in the hope of finding an inexpensive yet reasonably accurate method of chest examination. De Abreu (2) (3) first applied such a method to tuberculosis case finding in 1936 by using a small Contax camera and photographing from the fluorescent screen on 35 mm. film. Extensive work has been done in Rio de Janeiro by De Abreu and his associates and this work has served to stimulate interest in the method by many other men in Europe and in this country. Lindberg (4) (5) has made extensive studies with this small film and believes it better than direct fluoroscopy but not good enough to displace full-size film.

In Germany extensive use was made of the 35 mm. film by Janker (6), Ulrici (7), and others, but more recent reports indicate that it has been thought too small and the Holzknecht Clinic in Vienna (8) has adopted a larger size. The 35 mm. film must always be enlarged before it can be interpreted and this procedure in addition to being inconvenient, results in loss of detail because of exaggeration of screen graining as well as film grain.

Potter (9) (10), working in collaboration with the General Electric X-ray Corporation Laboratories, set out to produce a photo-roentgenograph sufficiently large to be read directly and yet small enough to make a real saving in film cost. After trying many sizes, a special camera and screen unit was developed which employs a film 4 x 5 inches in size which can be readily interpreted directly without enlargement, though an ordinary reading glass may be an aid in observing certain details in occasional cases.

The authors have been concerned with the clinical application of this latter method for the past several months in an attempt to evaluate its use as a case-finding tool.

The equipment used consists of a rotating anode tube capable of handling more than 400 ma. at 60 to 80 k.v., timed with an impulse timer. The camera-screen unit consists of a specially constructed fluorazure screen mounted at one end of a closed tunnel with the camera at the opposite end in a fixed focus, full open position. The lens, six inches in

diameter and of F 1.5 speed, is made on the same general principle as the Contax camera lenses only much larger. The films are carried in simple 4 x 5 inch double holders. The screen is set 50 inches from the tube target and exposures are made in from one-twentieth to four-twentieths of a second, depending on the thickness of the chest.

The first study (11) which has been extensively reported elsewhere concerned itself with the making of a full-size film and a small film of

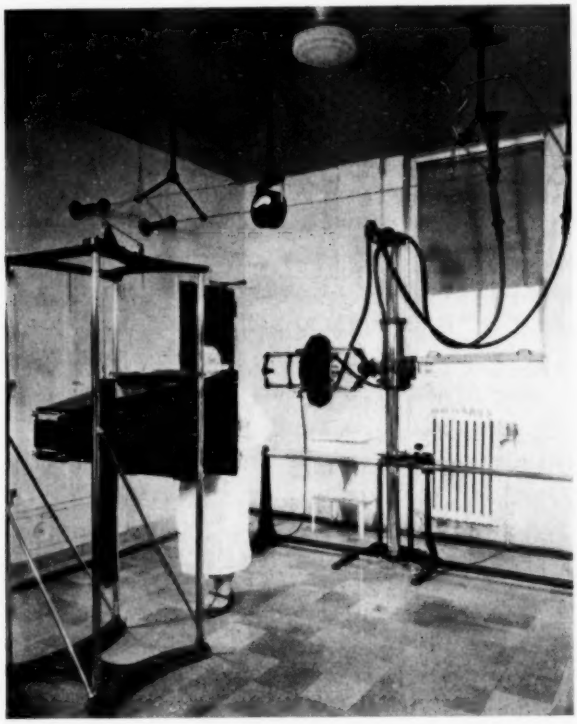


FIG. 1. Photo-roentgenographic equipment.

the same person for the purpose of determining how accurate the small film might be in relation to the large size. Accordingly 1,610 clinic attenders were examined with both films. The small films were interpreted entirely independently of the large ones and the readings correlated by a statistician, making the study as objective as possible.

Taking the 14 x 17 film as standard, there were 271 tuberculous lesions found of which the interpretation of the small film missed 5 entirely and called 5 others, other degrees of tuberculosis. Of these 5 others, 3 were

interpreted as lesions extensive enough to require further study, but 2 were called healed primary lesions and so would not be studied further. A fair appraisal then would indicate that the 5 complete misses and the the 2 healed primary foci should be recorded as misses making 7 out of 271 or 2.6 per cent error. The misses were all very small minimal lesions which while requiring follow-up were not severe. The principle reason they were missed was due to the lesion falling under a rib in the small film and being in the open on the large film.

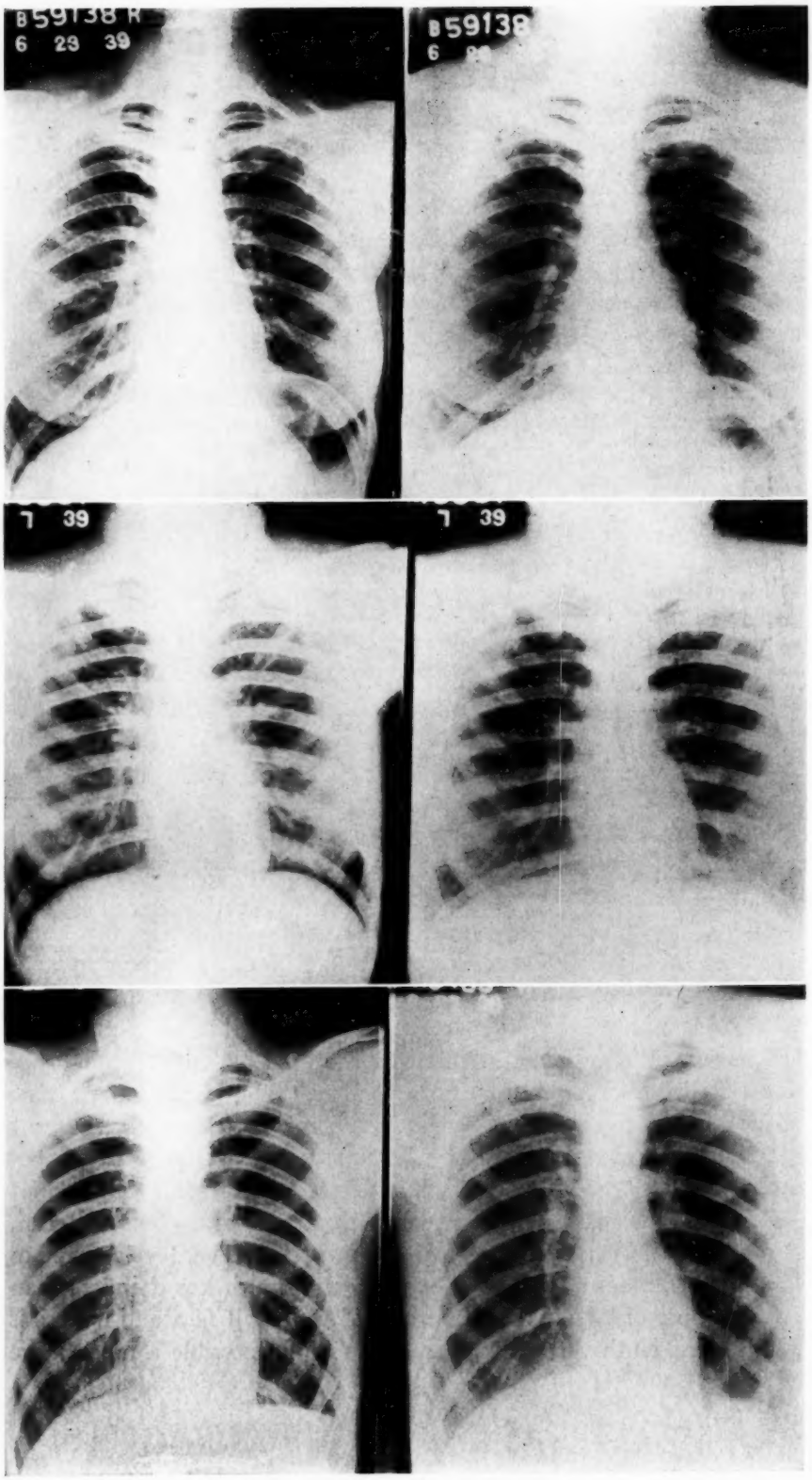
Active lesions in 1,610 clinic attenders examined with large and small films

DIAGNOSIS FROM LARGE FILM		SMALL FILM INTERPRETATION
Primary active	5	Complete agreement
Pleurisy with effusion	17	1 called dry pleurisy
Minimal active	117	5 called negative 1 called minimal healed, 2 primary healed
Moderately advanced	92	1 called minimal healed
Far advanced	40	Complete agreement
Total	271	

With improvement in technique and greater familiarity with the interpretation of the small film, the authors feel that this error can be made much smaller. When it is realized that the comparison was made with a full-size film made with a rotating anode tube at a fortieth of a second at six foot distance, the record seems good.

Having found the method quite accurate it was adopted for the examination of all admissions to the out-patient clinic and for the check-up of patients discharged from the sanatorium. An extensive experience, therefore, has been had in the use of the small film in this way, some 15,000 of them having been made. It has been interesting to note how many patients it has been necessary to call back for a large film either to clear up the diagnosis or because of a poor film. A recent check on 6,104 consecutive miniature films taken of out-patients revealed that 51 were called back for a retake on large films. This is only 0.8 per cent. The reasons for these retakes were in 28 tuberculous lesions whose extent or activity were in question; in 9 with unusual lesions; in 12 with technically poor films and in 2 the films could not be located.

The equipment can be operated rapidly and safely. In a test run, 73 persons were examined in sixty-five minutes. The development of these small films is simple and obviously uses much less chemical than a like number of large films. The cost of the small film and materials is about one-tenth that of regular film, making possible a much more



FIGS. 2–4

extensive X-ray service for the same material cost. The problem of handling, filing and storage is much simpler.

A further study using the miniature film as a survey method was made covering the women attending the prenatal clinics of the Department of Health. In a period of six months, 1,425 women were examined. In addition to the X-ray examination, all these women were tuberculin tested, using a single intracutaneous test with a 1 to 1,000 dilution of Old Tuberculin. One hundred and forty-four, or 10 per cent, of these failed to return for the reading of the test which is a common occurrence in tuberculin testing. They had all been X-rayed, however, and so were not lost. There were 2 active cases in this group, one moderately advanced and one far advanced, that might have been missed if only reactors had been examined by X-ray.

Prenatals tested who failed to return for reading of test but who were X-rayed 144 out of 1,425

Result of X-ray in this group

Negative	120
Primary healed	18
Moderately advanced, active	1*
Far advanced, active	1*
Suspicious	1
Nontuberculous conditions	3
	144

* 2 cases might have been lost through failure to complete test.

The remaining 1,281 had the tests read and 610 were positive, or 47.6 per cent. Among the 610 reactors there were 3 active cases, one primary active, one minimal and one moderately advanced. Among the 671 negative reactors there were 2 active cases found by X-ray examination, one primary active and one moderately advanced.

Obviously these figures are small and yet they suggest the possible loss from failure to return for the reading of the tuberculin test and the positive reactors that may be missed by using a single-dose method of tuberculin testing.

It will be noted that there were 7 active cases in the total group of

FIG. 2 (Upper). Comparison of 14 x 17 (right) and 4 x 5 (left) reduced to the same size. Minimal lesion upper left.

FIG. 3 (Center). Comparison of 14 x 17 film (right) and 4 x 5 (left) reduced to the same size. Minimal lesion upper right.

FIG. 4 (Lower). Comparison of 14 x 17 film (right) and 4 x 5 (left) reduced to the same size. Old pleurisy left base.

1,425 women, or 0.5 per cent, which checks quite closely with other surveys of presumably normal groups from the congested parts of the city.

Tuberculin tests and X-ray examinations—Prenatal group (miniature films)

RESULT OF X-RAY EXAMINATION	RESULT OF TUBERCULIN TEST		
	Positive	Negative	Total
Negative	512	598	1,110
Primary, active	1*	1**	2
Primary, healed	75	62	137
Minimal, active	1*	0	1
Minimal, inactive	2	1	3
Moderately advanced, active	1*	1**	2
Suspicious	3	4	7
Pleurisy, dry	5	2	7
Nontuberculous conditions	10	2	12
	610	671	1,281

* 3 with active lesions among the positives or .5%.
** 2 with active lesions among the negatives or .3%.

DISCUSSION

The possibilities of this method are numerous. Because of the low cost of materials it can be applied far more extensively than the usual methods of X-ray examination.

At present, to get the best results the high milliamperage technique must be employed which means that it is useful for large centrally located clinics principally. Because of the success attending the use of the experimental unit in the Tuberculosis Clinic at the Herman Kiefer Hospital, a second unit is being placed in a special survey clinic in a congested part of the city where the mortality from tuberculosis is high. It is planned to examine everyone in the area free of charge, at the rate of approximately 300 per day.

It will undoubtedly be possible very soon to have suitable equipment in portable form for making 4 x 5 photo-roentgenograms. Already considerable work is being done with a 200 ma. technique at 40 inches and $\frac{1}{4}$ second time. While these films are not as brilliant as those made with the higher milliamperage, still they are diagnostic to a large degree. If this technique proves practical it will make possible the use of portable equipment within certain current limitations which will greatly enhance the usefulness of the method for certain survey problems.

At the present time the small film has not been thought quite ade-

quate for following the treatment of patients in the hospital where the finest of detail is required in evaluating the application of the various collapse therapy procedures. For this purpose the best full-size films, frequently augmented by Potter-Bucky grid films and stereoscopic films, not to mention laminography, are needed. It may be possible, however, that with improvement which will undoubtedly follow, this method can later be applied to some of the tuberculosis hospital or sanatorium work.

Even now the miniature film has been found exceedingly useful in the follow-up of discharged patients. Its economy makes possible more frequent examinations of arrested cases. Most small changes can be detected with the 4 x 5 film and if there is any question the large film can always be taken. This offers, then, a definite measure of safety for the discharged patient in making possible the earlier detection of a reactivation, should it occur, through more frequent examinations by X-ray.

The photo-roentgenographic technique, using the 4 x 5 inch film and the high milliamperage technique, in addition to uncovering tuberculosis assists in finding many other pulmonary and cardiac conditions which, while not important as communicable diseases, are of great importance to the individual patient and his family and if discovered early often can be successfully treated. This is a very useful byproduct of this method of examination.

The authors are definitely of the opinion that the small film should only be used for the examination of large numbers on a survey basis and is in no sense to be thought of as a substitute in the finer problems of the diagnosis of chest diseases.

CONCLUSIONS

1. Photo-roentgenography with the 4 x 5 inch film is quite accurate when compared with the large film.

2. This type of examination can be used rapidly and economically in surveying large numbers of persons.

3. Photo-roentgenography can be applied directly without preliminary tuberculin testing with greater accuracy and, at the same time, economically.

4. The 4 x 5 inch film is a practical size for direct interpretation without enlargement and has decided advantages over certain other methods of X-ray examination either as to accuracy or cost or both.

5. Finally, the authors are satisfied that their experience warrants

the conclusion that photo-roentgenography of this type is a practical method for tuberculosis case-finding by means of surveys of large groups.

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ACUTE SILICOSIS[1]

Occurring in Employees of Abrasive Soap Powder Industries

R. J. RITTERHOFF

The clinical picture and pathogenesis of so-called acute silicosis has been adequately recorded in several papers, the most notable being that of Gardner (1) on the Gauley Bridge Workers. However, only 6 proved cases have been described in workers engaged in the manufacture of abrasive soap powders. Because of the paucity of reviews it is felt that a report of 2 cases will not be redundant, and will probably emphasize a few points not previously stressed.

In 1930, Macdonald, Piggot, Gilder, *et al.* (2) published 2 cases from Great Britain. This was followed in 1932 by a single case report by Chapman of Boston. The other reported cases, 3 in number, were reported from Great Britain in 1936 by Middleton (4). These latter patients had been employed at the same factory as those reported by Macdonald, Piggot and Gilder. The available salient data of these reports are summarized in table 1.

Reports of fatal and nonfatal non-necropsied cases of acute silicosis due to abrasive soap powders (table 2), while possibly of less value, illustrate many of the germane features of the clinical course and difficulties of diagnosis of the disease. Chapman, in his report of a necropsied patient, discusses 2 other patients in the same factory, one of whom was still living at the time of his report. In the same year, Kilgore (5) of San Francisco, reported 6 patients again from one factory, one of whom was still living at the time of publication. These latter cases, probably the least conclusive of all, were compiled from public records, employees, relatives and friends, after suspicion had been raised, and probably embrace almost all of those who worked nine or twelve months in the dusty part of the factory. Analysis of this company's soap powder revealed 90 per cent abrasive. The final clinical report is that of Middleton, who summarized the known fatal and nonfatal cases of silicosis, and the fatal

[1] From the Percy Shields Laboratory of the Hamilton County Tuberculosis Hospital (a sub-department of the Department of Medicine, College of Medicine, University of Cincinnati), Dr. John Skavlem, Medical Director, Cincinnati, Ohio.

TABLE 1

Autopsied cases of acute silicosis

OBSERVER	AGE	SEX	DURATION OF EXPOSURE	ONSET OF SYMPTOMS	LENGTH OF LIFE AFTER CESSATION OF EXPOSURE	CLINICAL FINDINGS	AGE AT DEATH	NECROPSY
1930 Great Britain Macdonald	14	Female	33 months	After 29 months exposure	4 months	Onset: Slight cough with pain in chest. Developed irregular pyrexia and evidences of right heart failure.	17	Massive confluent silicotic pulmonary fibrosis; no evidence of tuberculosis.
	15	Female	51 months	0	6 weeks	Low grade fever; evidences of terminal right heart failure. Chest X-ray: suggestive of miliary tuberculosis. Sputum negative for bacilli.	19	Discrete silicotic nodulation. No evidence of pulmonary tuberculosis.
1932 Boston, U. S. A. Chapman	26	Male	26 months	10½ months	11 months	Onset: Slight cough. Dyspnoea. Developed intercurrent pneumonia. Died 18 days after onset of pneumonia. Sputum negative for tubercle bacilli. X-ray diagnosis: Silicosis.	29	Confluent fibrotic zones in midlung fields. Emphysema at bases. Right ventricular cardiac hypertrophy (350 g.). Microscopic: Confluent silicotic nodules. Nonspecific bronchopneumonia. Focal areas of necrosis in liver. Foci of macrophages in splenic corpuscles.
1936 Great Britain Middleton	14	Female (Case 35)	Approximately 36 months	No data	7 years	No data	24	Massive silicosis of lungs and glands. Miliary silicosis of lungs, lymph nodes and spleen.
	16	Male (Case 42)	23 months	No data	20 months	No data	20 approximately	Far advanced pulmonary tuberculosis and silicosis.
	15	Female (Case 26)	45 months	No data	5 months	No data	19 approximately	Pulmonary silicosis. Tuberculosis in glands.

cases of pulmonary tuberculosis, which occurred in a group of 59 people employed in one factory in Great Britain. These cases of pulmonary tuberculosis of this group are summarized in table 3.

Case Reports

Case 1: White male, age eighteen, R. 278. Three months prior to admission the patient contracted an upper and lower respiratory infection which persisted for several weeks and then subsided. During this interval he noted precordial and epigastric pain which radiated to the right lateral chest wall, and which was exaggerated on deep inspiration. A private physician was consulted, who advised complete bed-rest. One month later the patient was admitted to the Cincinnati General Hospital for observation and study. The chief symptom at that time was dyspnoea. The physical findings were those of rheumatic heart disease with mitral stenosis and insufficiency and cardiac enlargement. A routine chest X-ray film disclosed "extensive lesions in the left and right upper lobes." One sputum examination was positive for acid-fast bacilli. Other laboratory findings were: erythrocyte and leucocyte counts, 5,200,000 and 15,200, respectively; haemoglobin 90 per cent (Sahli). The patient was subsequently transferred to the tuberculosis sanatorium.

There was no known contact.

At the age of fifteen, patient was employed by a local soap company. During his one year, and only year, of employment he worked as a mixer of soap powder, which consisted chiefly of sodium hydroxide and finely ground sand. Subsequent to his admission to the sanatorium, it was learned that there had been 2 cases of silicosis, one fatal, among the employees of this company several years prior to the patient's onset of symptoms. Following the discovery of these cases, adequate protection for the employees was rigidly instituted.

Physical examination: Blood pressure 115/65, pulse 100, respiration 24, temperature 99°F. The patient was a well developed, well nourished, mentally retarded white male not appearing acutely or chronically ill. The significant findings were confined to the thorax. A diffuse heaving impulse was present over the precordium, particularly in the third, fourth and fifth left interspaces, near the sternum. The point of maximum impulse was diffuse and approximately 10 cm. to the left of the sternum. The cardiac rate at the apex was 98 and the rhythm regular. The second pulmonic sound was accentuated and a soft blowing systolic murmur was heard at the apex. On percussion the heart was found to be 4 cm. and 11 cm. to the right and left of the midline in the fourth interspace. Examination of the chest revealed impaired percussion note over the apices of the upper lobes down to the second interspace and the fourth interspace anteriorly and posteriorly, respectively, with increased whispered voice and harsh breath sounds in the same areas. Occasional medium râles were heard over the apices, posteriorly. Over the right

TABLE 2

Fatal and nonfatal reported non-necropsied cases of acute silicosis

OBSERVER	AGE	SEX	DURATION OF EXPOSURE	TIME FROM LAST EXPOSURE TO DIAGNOSIS	LENGTH OF LIFE FOLLOWING CESSATION OF EXPOSURE	CLINICAL FINDINGS	X-RAY FINDINGS	COMPLICATIONS	STATUS
1932 Boston, U. S. A. Chapman	45	Male	8 months	52 months	52 months	Dyspnoea after 8 months exposure. Progressed until incapacitated. Pneumonia, after 3 years exposure. Final illness contracted 1 week before death—upper respiratory infection progressing into pneumonia. Sputum negative for tubercle bacilli.	Advanced silicosis, with cavitation. Upper two-thirds of right lung dense and mottled. Fan-shaped shadow extending into left lung field. Density with fluid level in left interlobar septum.	Pneumonia, type (?)	Dead
	27	Male	29 months	11 months	Living 4 months after diagnosis was made	Intermittent chest pains. Dyspnoea. Cough. Later, developing mucopurulent sputa negative for tubercle bacilli. Dyspnoea progressed, developed signs of right heart failure. Vital capacity 2.7 litres.	Chest clear. Heart enlarged to right and left.	Right heart failure	Ambulatory
1932 San Francisco Kilgore	70	Male	16 months	Not made	5 years, 8 months	No data of clinical findings.	No chest X-ray film.	No data	Dead. Coroner's necropsy: Terminal bronchopneumonia. Chronic myocarditis.
	50	Male	27 months	Not made	20 months	Had complained of chest condition. No other data.	No chest X-ray film.	No data	Dead. Death certificate signed, Myocarditis.

	36	Male	14 months	6 months (Tuberculosis)	Living	Dyspnoea, cough, haemoptysis. Tubercle bacilli in sputum.	Mottling throughout middle third of both lungs. And cavities.	Pulmonary tuberculosis	Receiving sanatorium care.
	31	Male	10 months	0	5 months	Dyspnoea, weakness, palpitation, cyanosis and signs of right heart failure.	Suggestive of miliary tuberculosis.	Right heart failure	Dead
1932 San Francisco Kilgore	31	Male	12 months	2 months	4 months	Dyspnoea, blood tinged sputa on two occasions, sensation of weight on lower chest on exertion. The symptoms started after 11 months exposure. Vital capacity, 2.5 litres. Sputum negative for tubercle bacilli. Developed anginal pain on effort, and signs of right heart failure.	Fine capillary fibrosis, most marked in apices, suggestive of disseminated advanced silicosis. Heart within normal limits. Terminally, had marked pulmonary fibrosis.	Right heart failure	Dead
	39	Male	24 months		24 months	After 20 months exposure, dyspnoea, loss of weight, orthopnoea, cough, night sweats; terminally, chest pains and haemoptysis.	Strands of fibrosis and mottling throughout both lungs. Density in the upper left and right hilar regions. No definite cavity formation. Annular shadows in upper right. Diagnosis: either tuberculosis, silicosis or fungus.	Tuberculosis?	Dead. Coroner's necropsy: Adhesions about lungs; pancarditis, type unspecified. Nephritis, splenitis, cirrhosis of the liver.
1936 Great Britain Middleton	17	Female	19 months	6 years, 1 month	Living	No data. Sputum negative for acid-fast bacilli.	Miliary pulmonary tuberculosis. Later, opinion that it was a disseminated silicosis.	Suppuration of a cervical node. Aetiology?	Living. Sputum negative 2 years after discharge.

base posteriorly the breath sounds were distant and percussion was impaired. Both diaphragms moved; however, the right leaflet only to a small degree. Three consecutive twenty-four-hour sputum specimens were negative on smear for acid-fast bacilli. Later, several guinea pigs inoculated with sputa were all negative for tuberculosis. Blood Wassermann—negative. Tuberculin test with 0.01 mg. OT was positive. Electrocardiogram showed a P-R interval of 0.02″ and notched P waves in all leads.

Dr. K. Dunham's roentgenological report reads: "The ribs on the right side are contracted. The trachea is drawn to the right. The aorta is obscured by a density in the upper left. The left border of the heart is difficult

TABLE 3

Known fatal cases of pulmonary tuberculosis at one factory in the manufacture of abrasive soap powder—Wales, England

SEX	AGE AT EMPLOYMENT	EXPOSURE DURATION	TIME FROM LAST EXPOSURE TO ONSET OF PULMONARY TUBERCULOSIS	KNOWN DURATION OF PULMONARY TUBERCULOSIS	AGE AT DEATH
Female	14	9 years	?	4 months	23
Female	14	1 month	7 years	10 months	22
Female	14	41 months (2 periods of employment—Free interval of 19 months)	Negative	1 month Sputum never +. Clinically considered as tuberculosis?	19
Male	44	33 months	Negative	1 month	47
Female	14	33 months	Negative	Several months	17
Female	14	13 months	Negative	5 months	16
Female	15	32 months	5 years		22
Male	15	10 months	4 years	10 months	21
Male	15	23 months	5 years	6 months	23
Female	14	10 months	2 years	2 months	17

to delineate from the dome of the diaphragm, which is only made out by gas in the stomach. The right dome of the diaphragm is obscured and indefinte due to density in the lower lobe. The pleura is thickened over the left upper and entire right lung. Small calcified nodules are present in both upper lobes. There is extensive mottling throughout the upper right lobe and to a lesser degree throughout the middle and lower right lobes. On the left side there is a large pneumonic area involving the first and upper branches of the second interspace trunks. There is some emphysema at the left base. These films suggest a previous history of pleural effusion on the right, and the development of a basal type of pneumonic tuberculosis, secondary to the pleural effusion, because of the reported presence of acid-fast bacilli in the sputum prior to ad-

mission. However, in view of the history of exposure to finely ground sand, the general diffuse densities throughout both lungs must be considered as due to silicosis."

Course in the hospital: Patient remained at total bed-rest for three months, during which time the physical and roentgenological findings remained the same. However, there was a low grade intermittent fever. The cardiac findings were essentially the same, except for a presystolic murmur at the apex, which was first noticed three months after admission. Because of very small amounts of either serous or mucous sputa which were consistently negative for acid-fast bacilli, the patient was transferred to the "up ward" and permitted moderate activity. During the final five months of life the chest findings were unchanged and the patient was afebrile. Dyspnoea on slight exertion became more marked, so that during the last few days he was put on absolute bed-rest. At this time fine râles were elicited at the right base posteriorly. On the afternoon prior to his death, the patient complained of precordial pain; however, after codeine he felt fairly comfortable and had no complaints. At 6:45 a.m. the following day, he was found dead.

Necropsy by Dr. J. W. Leichliter, two hours postmortem—T–33–19. The domes of the diaphragm extended to the level of the fourth right interspace and the sixth left rib. The thoracic viscera were in their usual positions and relations. However, the enlarged heart, the greatest transverse diameter being 17 cm., extended 5.5 cm. to the right of the midsternal line; 200 and 500 cc. of clear colorless fluid were present in the right and left pleural cavities, respectively. Several thick, tough, pleural adhesions were present in the cupolae. The pericardial cavity, the linings of which were smooth and glistening, contained a normal amount of clear fluid. The heart was markedly enlarged (weight not recorded), being most evident in the right auricle and ventricle. The cardiac measurements were: greatest transverse diameter, 17 cm.; tricuspid valve, 14.5 cm.; pulmonic valve, 105 mm.; mitral valve, 160 mm.; aortic valve, 70 mm.; right and left ventricular walls, 2 and 11 mm., respectively. The thin transparent valve leaflets presented no abnormality. All chambers were dilated, being most marked in the right heart. The coronary arteries and their ostia presented no abnormality. The lungs and trachea were removed intact, inflated and then X-rayed.

The posterior half of the contracted upper lobe of the left lung was of stony hardness. Anteriorly, over both lobes a few emphysematous blebs were present. The interlobar fissure was obliterated by dense adhesions. The upper lobe was condensed into a very small mass. The lingual tip was sharply demarcated as an almost separated lobe by a dense constricting band of scarred pleura. A small accessory lobe projected from the mesial surface of the lower lobe. On section the left upper lobe was found to be completely occupied by a dense tough mass of black scar tissue, in some places presenting a smooth,

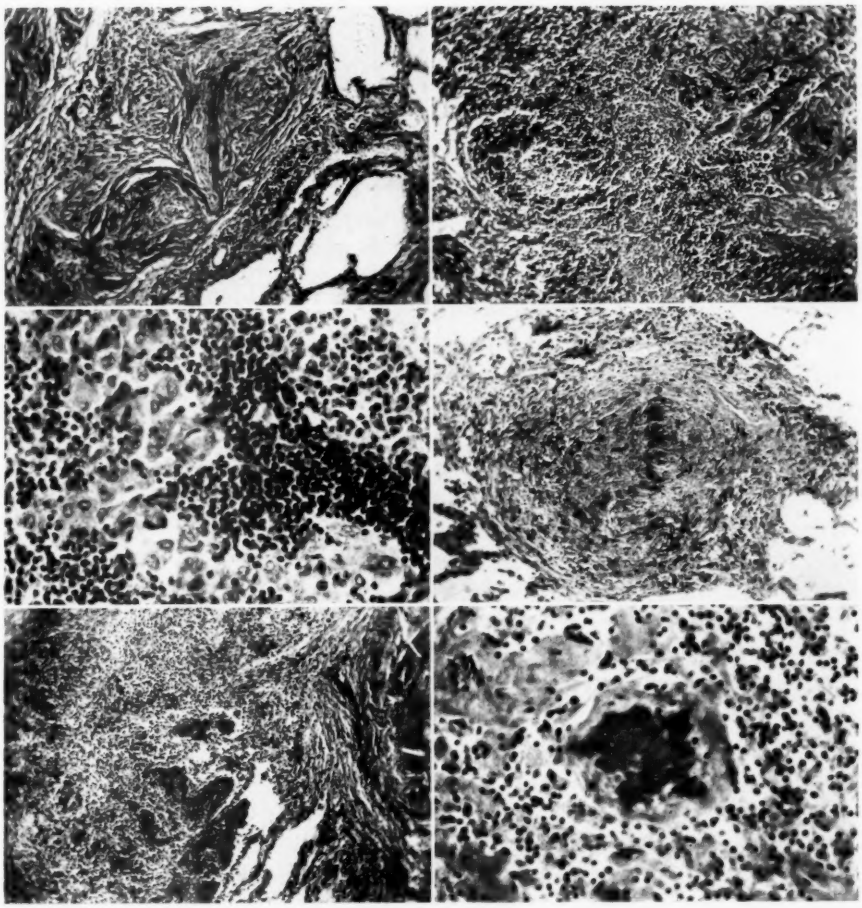
homogeneous cut surface; elsewhere it ran in denser, pearly strands. Approaching the lingual tip and the base of the upper lobe, the fibrous tissue faded out gradually and was interspersed among islands of spongy, elastic, froth exuding areas of emphysema. The separation of the upper and lower lobes was not complete, as the fibrous scars bridged across in the posterior portions of the lobes. External to the main left bronchus there lay a crescent of partially calcified tissue, lying in an oblique plane anteroposteriorly, with the open segment facing laterally. The lower four-fifths of the lower lobe showed only a coarse spongy emphysematous appearance.

The upper lobe of the right lung appeared even more contracted than its mate on the left, and its upper half presented a similar stony hardness. A markedly thickened parietal pleura adhered tightly to its surface and scar tissue obliterated the interlobar fissures between it and the lower and middle lobes. Mesial to the upper lobe there was a large group of mediastinal lymph nodes of various sizes tied together into a fibrotic knot. There were moderate emphysematous changes on the anterior surface of the middle lobe. An ear-like projection of emphysematous lung sprang from the lateral border of the middle lobe and appeared like an appended accessory lobe. Moderate sized emphysematous blebs were visible on the anterior and mesial surfaces of the lower lobe. On section of the right lung, confusion was caused by a large mass of enlarged confluent nodes, occupying the normal position of the upper lobe. This tissue was differentiated only with difficulty from lung. Careful examination showed the completely compressed and scar-distorted upper lobe lying below and mesial to this mass of nodes. Fibrous black scar tissue fused the upper and middle lobes into an almost inseparable union. The pleura over these lobes was thicker than that on the left and had a pearly-gray shiny appearance. Only a moderate amount of scar tissue was present in the lower lobe, which again presented a coarse spongy appearance. Surrounding the hila, there was a mass of enlarged, peculiarly colored lymph nodes, similar to the group found over the right apex. Careful search revealed no evidence of cavitation or caseation which might be caused by tuberculosis. No Dunham "fans" or Ghon foci could be found, and the only evident calcification was in the one area described above.

The remainder of the viscera were remarkable only for evidences of chronic passive congestion.

Microscopical diagnoses:

1. Massive confluent pulmonary silicotic fibrosis with marked chronic pulmonary emphysema (figure 1).
2. Focal silicotic nodules in the tracheobronchial lymph nodes (figure 2).
3. Metastatic silicotic nodulation in the spleen and liver (figure 3).
4. Toxic myocardosis and evidences of chronic passive congestion of the viscera.
5. Slight aortic atherosclerosis.



FIGS. 1–6

FIG. 1 (top left). T–33–19. Apex of left upper lobe. Confluent hyalinized silicotic nodular fibrosis, with marked chronic pulmonary emphysema and fibrosis of the alveolar walls. Small foci of pigmented macrophages above and below the central nodular areas of fibrosis.

FIG. 2 (top right). T–33–19. Tracheobronchial lymph node. Confluent diffuse and perivascular areas of silicotic fibrosis on the right side of plate. A follicle shown on the left contains a hyperplastic germinal center. Throughout there is moderate pigmentation and hyperplasia of the reticuloendothelial cells.

FIG. 3 (center left). T–33–19. Spleen. Confluent foci of hyperplastic reticuloendothelial cells scattered throughout the sinusoids. In the upper right corner of the plate there is a markedly hyperplastic germinal center of a splenic follicle.

FIG. 4 (center right). T–38–93. Apical region of the upper lobe of the right lung. A discrete hyalinized silicotic nodule with deposition of pigment and a peripheral rim of active fibroblasts and macrophagic reaction. Marked chronic pulmonary emphysema and thickening of the alveolar walls can be seen peripheral to the nodule.

FIG. 5 (bottom left). T–38–93. Lower lobe of right lung. At the extreme right there is a small portion of a silicotic nodule. Adjacent to this, occupying the central area, is a zone of caseous tuberculous pneumonia. At the extreme left is the wall of a caseous bronchus. The reaction in these latter two areas is predominantly macrophagic with a moderate number of polymorphonuclear leucocytes. Numerous acid-fast bacilli were present in the lesions.

FIG. 6 (bottom right). T–38–93. Tracheobronchial lymph node. Silicotic nodule with central hyalinization. Coarse bands of fibrosis and moderate hyperplasia of the reticuloendothelial cells surround the nodule.

Case 2: Y.28. White male, age twenty-nine. Six months prior to admission the patient noticed weakness and fatigue, being most marked in the afternoon. One month later the patient contracted an upper respiratory infection which persisted for several weeks. Because of no improvement and the development of a productive cough, a chest X-ray film was taken. No lesions, however, were discernible. After eleven weeks of partial activity and bed-rest, he returned to work. Within two weeks, weakness and productive cough recurred; also slight dyspnoea and right chest pain became prominent symptoms at this time. A chest X-ray film at this time, interpreted by another roengenologist, revealed "clouding in the posterior part of the right chest just above the diaphragm, probably encapsulated pleural effusion, and nodular infiltration around the hilar areas; apices clear." A subsequent sputum examination was "very positive" for acid-fast bacilli. On admission to the sanatorium several weeks later, the patient was, subjectively, improved.

The patient had visited an individual with pulmonary tuberculosis several times three years prior to entry to the sanatorium.

Patient had been employed in a local soap company for nine years, six and one-half years as a general laborer on various jobs and the last two and one-half years as a mixer in a soap powder department. Employees in this department used provided respirators. Analysis of this powder revealed 8 per cent Na_2SiO_3; however, no free silica.

Physical examination: Temperature, 99; pulse, 85; blood pressure 110/70. Patient was a fairly well developed, chronically ill white male, twenty-eight years of age. The significant physical findings were confined to the chest. Left lung: roughened and accentuated breath sounds at the base, fine and medium râles posteriorly along the vertebral border of the scapula. Right lung: percussion note dull to flat over the inferior two-thirds, diminished tactile fremitus; pectoriloquy, amphoric breath sounds, and aegophony over the inferior half posteriorly and laterally; fine râles at the base of the upper lobe anteriorly; fine, medium and coarse râles over the inferior half posteriorly; fixed right diaphragm.

The admission X-ray film was read by Dr. K. Dunham, as follows: "The right border of the heart and right dome of the diaphragm are obscured by a heavy density over the lower lobe. The left dome of the diaphragm is flattened suggesting pulmonary emphysema. Right lung: there is heavy thickened pleura over and below the upper lobe. Below this there is a homogeneous density which might be fluid. In the middle lobe there is indistinctly seen an area of decreased density which might be a cavity which, however, may only be a pleural change. The upper lobe is studded with a very fine mottling similar to a miliary tuberculosis, but miliary tuberculosis is not diagnosed. Left lung: slight changes in the linear markings of the vertebral trunk. The trunks to the upper lobe are heavier than average, but a "fan" is only suggested in the apex. There is a curious density in the hilar area which suggests a

caseocalcareous lymph node, but this is not diagnosed." X-ray diagnosis: "Pleurisy, the aetiological factor of which is undetermined."

Three consecutive twenty-four-hour sputa were negative for acid-fast bacilli. Serological tests for syphilis were negative. Sedimentation index, Westergren method, 85 mm.

No pleural fluid was demonstrable on repeated thoracocenteses. Bed-rest alone was responsible for clinical and roentgenographic improvement, so that during the tenth month of hospitalization he was transferred to the "up ward." At this time sedimentation index was 44, and 8 monthly sputum examinations had been negative, having been positive only once during the second month. At this time an X-ray film revealed "clear left lung field and a thickened pleura over the entire right lung." One month after transfer, following the subsidence of acute tonsillitis, the patient developed a nonproductive paroxysmal cough, foul breath, malaise, and after several days, high fever and marked toxaemia. Physical and X-ray findings suggested a right hydropneumothorax. After removal of 300 cc. of thick, malodorous pus, X-ray examination disclosed a cavity in the right first interspace; right upper lobe, adherent to the anterior chest wall; right pyopneumothorax, and caseous tuberculous bronchopneumonia of the entire left lung. Laboratory data at this time were: sedimentation index, 102; leucocytic count, 15,500; differential leucocytic picture 47 per cent stab cells, 23 per cent segmented, 13 per cent juvenile leucocytes, 5 per cent lymphocytes and 12 per cent large mononuclear leucocytes. Open right thoracotomy was done, and the patient expired twelve hours later.

Necropsy: T–38–93 (limited to examination of the lungs only) Dr. B. S. Wells. Twelve hours postmortem.

"On removing the symmetrical breast plate the thoracic viscera were in their normal positions and relations, except for an empyema pocket overlying the posterolateral aspect of the greater portion of the right upper lobe; 200 cc. of foul, purulent fluid, and a large rubber tube drain extending through the thoracotomy wound, were present in this pocket. The remainder of the right pleural space was obliterated by dense, tough gray adhesions. The parietal pleura over the empyema cavity was corrugated, greenish-gray, lusterless, and 1 cm. in thickness; while the visceral pleura presented essentially the same picture, it was only 0.5 mm. in thickness. Several thin, easily broken, white bands were present over the apex of the left upper lobe. Bronchopleural fistula was not demonstrable. The right lung was slightly collapsed, firm and boggy. Numerous small and large nodular areas were palpated throughout the lung substance. The left lung was well expanded and generally crepitant, with numerous small nodular, noncrepitant areas throughout. The apex of the left lower lobe was noncrepitant, somewhat rubbery and firm.

On section the right upper lobe was generally gray, firm, subcrepitant and studded with discrete and confluent, soft and firm, gray and grayish-green

nodules, 1 to 5 mm. in diameter. Between some of the nodules a few small salmon-pink crepitant areas of apparently normal lung tissue were seen. No cavities were seen. The right middle lobe on section was generally salmon-pink, crepitant, to subcrepitant, normal in consistence, and presented several scattered discrete and confluent, grayish-green nodules, 2 to 3 mm. in diameter. The right lower lobe on section was generally noncrepitant, boggy, slightly wet and gray to light red in color. The bronchus to the apex of the right lower lobe terminated in a thin-walled, grayish-green cavity, 3 cm. in diameter, which contained a small amount of moderately thick, foul, grayish-green debris. Just above the anterior margin of the base of this lobe was a similar cavity, 2 to 2.5 cm. in diameter. The lung tissue adjacent to these cavities was not tough and fibrous, but was instead blackened, friable and necrotic. Throughout the right lower lobe, especially in the lower half, were numerous discrete and confluent, grayish-green, soft, irregular areas, 2 to 12 mm. in diameter, which apparently were abscesses. A few scattered firm, gray and grayish-green nodules, 2 to 4 mm. in diameter, were seen. The left lung on section was generally moderately reddened, slightly wet, crepitant to subcrepitant, and studded throughout with innumerable discrete and confluent grayish-white soft and firm nodules, 2 to 5 mm. in diameter. These nodules were mainly in close relation to the bronchial trunks. The apical portion of the left lower lobe differed from the rest of the left lung in that the tissue was gray, very firm, and studded with numerous firm, green, rubbery, sharply demarcated nodules, 4 to 8 mm. in diameter. The bronchial mucosa was reddened, swollen, and slightly granular in areas, especially in the right lower lobe.

The tracheobronchial lymph nodes were slightly enlarged, black and rubbery. A large focal area of calcification was present in one of the left bronchial lymph nodes.

Microscopical diagnoses:

1. Acute tuberculous fibrinous pleuritis (empyema), superimposed mixed infection; acid-fast bacilli, gram-positive spore formers, gram-negative bacilli, and gram-positive cocci. (The same organisms were found antemortem.)
2. Disseminated discrete and confluent miliary pulmonary silicotic nodules (figure 4).
3. Diffuse acute caseous tuberculous bronchopneumonia with recent cavitation (figure 5).
4. Chronic active interstitial pneumonitis with associated pulmonary fibrosis;
5. Chronic active pleuritis and pleural fibrosis;
6. Chronic pulmonary emphysema;
7. Marked pulmonary atherosclerosis;
8. Silicosis and caseous tuberculosis of the tracheobronchial lymph nodes (figure 6)."

Because of the character of the microscopic lesions, the history of exposure to a dusty atmosphere, and the litigious tendencies of the deceased's family, the occupational history was reinvestigated and microscopical sections were sent to Dr. Leroy U. Gardner of the Saranac Laboratories, who made the following comments:

"It is unfortunate that larger pieces of tissue were not available for analysis, so that large sections, 3 to 4 inches in diameter, could be prepared to demonstrate the distribution of the lesions and to subject to chemical analyses. However, I appreciate the limitations placed upon you by the autopsy permit.

A section of a tracheobronchial node reveals many perfectly typical hyaline fibrous silicotic nodules and the lungs show a few small lesions of this nature in addition to a diffuse cellular fibrosis. Changes of this type have been found in the lungs of other soap powder makers.

From the evidence at hand I think you would be perfectly justified in adding this case to the list of "soap powder rapid silicosis cases" similar to those described by Chapman, Piggot, Gilder, and others.

The X-ray films of such cases do not usually show characteristic nodulation."

After notification of the company officials of the final necropsy diagnoses, the time and production records of the deceased were checked for his entire period of employment. It was found that the patient had a maximum of one hundred days' exposure over a four-year period in another soap powder department where a different product was made. Analysis of this powder, the information being supplied by the company, revealed 60 per cent free silica, 30 per cent Italian pumice, and 10 per cent "kettle soap." This exposure period was prior to the inception of definite control of dust exposure, such as dust counts, efficient hood respirators, adequate ventilation, which has been in effect for the past five years; also, this exposure terminated three years prior to the onset of his first symptom.

COMMENT AND SUMMARY

The exposure history of these 2 cases, one hundred days, and twelve months, is considerably less than that for the reported cases, autopsied and clinical, which averaged thirty-six months and seventeen months, respectively. Also, the duration of life after cessation of exposure is considerably longer, four years, than the average for the two groups, which was twenty-six months and twenty-nine months, respectively. However, one of Middleton's cases lived seven years after cessation of exposure, and three of the group of clinical cases reported were still

living at the time their case histories were published. Various investigators originally proposed the theory that in some way alkalies promoted the solubility of silica and thereby the "acuteness" of the reaction. However, Gardner (1) and Lanza (6) believe, in view of the fact that acute silicosis is found in other industries in which alkalies are not used, that the "acuteness of the reaction is logically explained on high concentrations of fine, free silica used in the manufacture of soap powders." Lanza (6) states that the term acute silicosis might best be reserved for only those cases showing discrete nodulation and that those showing massive silicotic fibrosis should not be included, thereby placing the diagnosis on a histological basis rather than on the basis of length of exposure, which was the original criterion. This, however, would automatically eliminate those cases in which secondary infection masks the lesions, and those cases having had massive exposures, which may alone produce confluent silicotic fibrosis, as is suggested by these cases in the soap powder industry. For, out of 6 proved reported cases, 4 had no history, bacteriological or necropsy evidence of tuberculosis and of these, 3 had massive confluent silicotic fibrosis. Tuberculosis, when present as a complication, was of the exudative caseous types, as deduced from their rapid fatal courses, rather than fibrocaseous or proliferative with slow progression or healing, which would be essential to produce and modify massive confluent silicotic fibrosis.

Gardner, in his experimental work, has found what he terms "metastatic silicotic nodules" in the spleens and livers of guinea pigs which were receiving massive doses of fine silica particles. It is interesting to note that this same lesion is present in our first case and in 2 cases described by Chapman (3) and Middleton (4), all of these cases being of the massive confluent type. These "metastatic" lesions are foci of macrophages, which do not show the typical histology of silicotic nodules and may be areas of reticuloendothelial hyperplasia rather than true metastases.

Failure of the right ventricle was noted clinically in 2 of the autopsied cases, and evidence of right ventricular hypertrophy at necropsy in another. Case 1 of the present report presented, clinically and pathologically, evidence consistent with the diagnosis of *cor pulmonale*. Of the clinical reports, 3 of the 9 cases were felt to have definite evidences of right heart failure. In a recent publication Gardner (7) states that it is felt that silicosis in and of itself is not sufficient cause for the production of disease of the right heart, and that when it did occur it could

usually be explained on some other basis, such as previous cardiac damage or pulmonary vascular disease. This, however, would not seem to be true in these cases for their ages at death were thirty years or lower, which should rule out degenerative changes in the cardiovascular system, and no mention of cardiovascular disease, other than right heart failure, is made. It would seem, then, particularly in this group, that embarrassment to the right ventricle, with or without *cor pulmonale*, is a not infrequent complication, which is most prone to develop in cases having areas of massive fibrosis and marked emphysema; and that this complication cannot be ascribed to previous cardiovascular disease.

Photomicrographs were made by Joseph B. Homan, of the Medical Art Department of the College of Medicine, University of Cincinnati.

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EDUCATION OF THE TUBERCULOUS PATIENT[1,2]

From the Point of View of the Social Worker

ADELE SHIMAN TROBE

In considering the topic, "Education of the Tuberculous Patient in the Sanatorium", we necessarily ask, "Why must he be educated?" The patient in the sanatorium is sheltered, under continuous supervision, getting more adequate care than available at home. Why add to his worries with additional knowledge? The less he knows the better off he will be.

There are manifold reasons, however, for our concern with this problem. In the disease tuberculosis, the patient must perform the major portion of the cure. The chronic nature of the illness requires a complete readjustment of the personality and of the social situation. The patient must feel convinced that this change is necessary. Besides it is economically sound to educate the patient about himself and his disease, looking towards the future when he is to continue his cure at home. I think here of two tuberculous patients of different races, religious faiths and backgrounds, who married after their discharge from from the sanatorium. They had, however, one thing in common—they knew how to live in the same way. They were similarly educated in the sanatorium.

Patients must also learn in the sanatorium, from competent authorities, to combat the often destructive information gleaned from other patients and lay friends and relatives. In these ways education is primarily aimed at supplementation of physical restoration, toward return to the community of a sound personality as well as sound lungs.

What do we mean by education? Possibly what we generally imply here is information about tuberculosis. What is it? How does it manifest itself? How is it acquired? How is it spread? How is it treated? What are the routine and length of cure? What is the prognosis? What are the possibilities for return to normal life? What

[1] From the Committee for the Care of the Jewish Tuberculous, New York City.

[2] Presented before The Nursing and Social Service Section at the Tuberculosis Sanatorium Conference of Metropolitan New York, January 22, 1940.

are the facilities and means of care? What agencies are interested, and how can they help? What must the patient do? What *can* he do?

Just which of these questions can be answered and how fully they can be answered will depend, of course, on the patient himself and on his own physical condition.

Vocational guidance and initial training of the patient must also be included in our concept of education. This will be correlated not only with the physical capacity of our patient, but also with his own native abilities, his educational and occupational background and his personal outlook upon his future. It may comprise work in the sanatorium, occupational therapy, or courses there on the public address system, in classes from teachers or through correspondence.

The patient also must learn to adapt himself to his new situation toward acceptance of his illness without retreat into it, and possibly, towards a changed economic, vocational and social future. The need for discussion of his problems in this area will depend on his first reactions to tuberculosis and his personality make-up.

The function of the social worker in these three types of teaching—medical, vocational and adjustmental—will depend, of course, upon the sanatorium set-up, as well as upon the patient. Superficially one might say that the doctor and the nurse were responsible for the medical aspects. But we, who know how busy the nurse in a sanatorium is with her numberless tasks, understand that she is unable to give very much attention to this problem. The same is also true of the doctors in most of our large public institutions. Some sanatoria attempt to meet this problem by periodic lectures to the patients, and while this method has advantages, and can benefit the curious and aware patient, not all can be reached in this way, nor can all doubts and questions be answered. The social worker often is made aware of a patient's need for information in her contact with him and can arrange for individual attention for him from the proper medical authority.

The vocational counselor, occupational therapist or adult education director may be the person primarily concerned with the vocational aspects of education, but more often than not they are not even on the staff. Often, if there is an occupational therapy department, it is under such pressure to produce suitable articles for sale that its staff has its hands tied with regard to centering on the patient's problem rather than on an administrative one. The social worker must be instrumental in referring patients who can be most benefited by the services available.

She also can help the person doing the vocational guidance by sharing her knowledge about the patient with him. If she alone must do the job, there are certain plans she can work out with him herself by consulting the community agencies, such as schools, libraries, guidance and employment services. For one college student, for instance, the social worker was able to secure French text-books so that he might teach other patients and keep up his skills.

The social worker has the largest share of responsibility for the third aspect, emotional reorientation, although there are institutions where she may refer some of the more serious problems to the psychiatrist. Case work service which deals with the question why a patient *cannot* learn is, of course, the inherent job of the social worker.

Some of the teaching rather than being direct with the patient, is indirect with the husband or wife, the mother or father, the sister or brother. Sometimes it is the nurse, the private physician, the staff physician or other agency case worker to whom we must interpret the situation so that they can handle the patient more realistically in their work which often comes under the classification of "education," too. The sanatorium social worker confers daily with these interested associates of the patient obtaining their participation in the teaching process. In one case the doctor found a young fellow insistent on going home against medical advice. After several interviews with the patient, the social worker discovered that underlying fears as to his future, and his identification with another patient who had had the same treatment, were what was driving this boy. This was interpreted to the doctor, who, armed with this knowledge, was better able to handle his part of the educational process.

We might consider who is this patient? What are the psychological factors and characteristic situations present making him different from other patients?

I think first of David Harris, a man of twenty-nine, successfully employed in the accountancy field, who planned with his wife to have a family. Upon becoming pregnant, Mrs. Harris gave up her job as secretary to a business executive, and suddenly, as they looked forward to the culmination of their hopes and plans, David had a haemorrhage and was shipped off to the sanatorium. Not only did he feel a complete loss of security, but he felt guilty about his desertion of his wife at such a critical time. He worried about what was going to happen to their child, he was concerned that his wife might have been infected too, and

he did not know how he would be able to reëstablish his home again. These threats to his security, the fears relating to his frustrated plans, to separation from his family and the plight of his dependents are common to hundreds of other patients and naturally delay their adjustment to their disease. Unfortunately, David was one of these so-called model patients, who are well behaved and submissive, and so are apt not to receive the amount of service which their actual situation may call for. From our knowledge of psychiatric principles, and from what often happens to these patients, we know that these are frequently actually the most disturbed patients, who need the most attention to prevent later breakdowns. They may have inhibited all the naturally resentful and discouraged feelings they must have had during the traumatic experience of learning of their tuberculosis, without healthily assimilating these feelings in realistic relation to the rest of their life pattern.

Another patient, Evelyn Lord, was twenty-seven, single and independent when she broke down with tuberculosis. She had previously helped to support the families of married sisters. Now that she was dependent, her relatives and friends were deserting her; some guilty because they could not help, others subjecting her to the social ostracism too often the fate of the tuberculous because of the fear of its communicability. No wonder this girl dreaded facing the world again.

The indefiniteness of the prognosis and uncertainty as to the future of this illness handicaps the social worker in giving assurance and the patient in accepting it. Mrs. Simon, who had a minimal lesion, and an effective pneumothorax, at first could not believe that her stay at the sanatorium was to be indefinite. She kept postponing definite plans for her children in the hope that she would be home soon, and only time and the social worker's assurances of help in planning on discharge taught her that it might have been wiser to break up her home earlier, both for the children's benefit and her own peace of mind.

At the sanatorium we also have to cope with the prior assurance of a well meaning private physician to his patient that she will only have to stay for three months, hoping in this way to expedite her departure to the sanatorium. This was particularly difficult for Anna, a patient who never completely readjusted to the idea that she might have to stay longer, despite such suggestions on admission. She fought the idea with tears and as the months wore on, became so hysterical that she only could be quieted with sedatives. The social worker, in frequent visits to her, discovered that her main difficulty was concern over losing her husband

of six months' standing. Although the worker was able to arrange certain temporarily effective moves, such as change of room-mates and stimulation by the occupational therapist and other staff members, they had no permanent value in alleviating her disturbance, because this girl was really in need of psychiatric service. This was necessary because it appeared to the social worker that her fear of losing her husband was not realistic since he remained devoted to her. Her present emotional upset, however, seemed related to her childhood experiences and possibly to early concern about her adequacy with men.

Reëducation is also necessary with the patient who comes to the sanatorium obsessed by the hopelessness of tuberculosis. The other attendant changes in his situation have helped give him little will to live and to get well. Education may mean here, as it did for one boy, Tom, permitting him to express his feelings about it. The social worker saw him frequently, learning to know him and discovering why he was reacting in this particular way, while another might overcompensate in the other direction. She learned how he had met other defeating situations and overcome them. He was led to talk of his hopes and his plans. He took vocational tests which reëmphasized his best abilities, giving him more self-confidence. A correspondence course was finally arranged for him, and through his achievements in it, he regained a purpose and was reëducated to a better orientation to his illness.

Some patients have been in so many institutions that they have become cynical, or they cling to their ill health, or they think they know all that there is to know about it, covering up real feelings of despair.

Others come to the sanatorium with all the proper preparation and, on arrival, express curiosity about their illness as if they had never been told anything about it. We find that when they were given this information first they were so upset at hearing the diagnosis that they could not listen. Similarly the unreasonable and demanding patient is so dominated by his feelings that his intellectual grasp of the situation is slowed and twisted, and rationalization and complete unwillingness to understand result.

Negative educational factors, however, are not only existent prior to admission. During the cure the presence of other patients may have a negative, as well as positive, effect. Patients of long standing try to gain status with new patients by detailing intricacies and discouragements of their own disease. The aforementioned patient who was counting on a three months stay was thrown into turmoil by the sarcasm

of fellow patients over her confidence. Sometimes, no doubt, the presence of other cheerful patients who are getting well and leaving is an encouraging sight. This is particularly beneficent in a sanatorium where there are not as many very sick patients as in a hospital. Naturally in the latter the problem is not doubled, but quadrupled by this factor. It took months for the patients to forget the friend two beds down who suddenly became psychotic, or the pretty young girl in the next ward who died. Often the doctor thinks that everything has quieted down after these episodes, but a year later the social worker will pick up some after effects of the traumatic experience in her longer and more intensive contact with the patient when his fears are brought into the open and are reëvaluated in free discussion.

What is the routine of the social worker's job, and how does her rôle as educator fit into it? We find that at Montefiore Hospital Country Sanatorium, for instance, the nurse may start the patient off, outlining the routine, the rules for precautions and the initial procedure. The patient supervisor gives the patient a copy of the rules, describes the social setting, the social service, the library, the occupational therapy department, entertainments and movies, arrangements for passes, the store, the barber, the tailor and other facilities. The doctor examines the patient the first week and confers with him at the end, answers questions, explaining the recommendations, making few promises and no guarantees. The social worker then sees the patient for the first time in the sanatorium. He has already been seen a few times in the city by the district worker and prepared for his stay. She asks him how he thinks she can be helpful to him at the sanatorium and discusses just what she is able to do. She iterates her interest in him and his family and explains that the worker in the city will be in close touch with them. He should feel free to come in to discuss with her anything that concerns him. Sometimes, because of the suggestion by a district worker, the social worker leads him on to discuss a problem noted in the city office, pointing out that she would be glad to follow it up with him in later interviews. It is often necessary to emphasize this interest of hers in his psychological and social problems, since patients, like many ordinary mortals, are accustomed to thinking of social workers as benevolent ladies whose sole job it is to give out clothing and money.

After this first interview, there may be many reasons why she sees the patient, but almost half of the time is devoted to the rôle as "educator". Probably more time is necessary, but most social workers are responsible,

too, for a great many administrative duties. These interviews may deal with physical factors. The patient does not understand why he must stay, why he must have therapy, why he needs glasses or dental work, and he wants an opportunity to discuss the situation and air his opinions. The social worker knows that he has been told the reasons for these things and ostensibly "educated," but he needs an opportunity to have a sympathetic listener to help him unravel his feelings and make his own decision, so that the education can take effect.

The patient also must be reassured that the social worker has confidence in his rehabilitation; that agencies have been established on that premise. He can be started on the road to recovery with help in vocational planning. We have found that the assurance that our social service will be interested in him for five years following his discharge or as long as necessary, and that there will be continuity of care, as well as possible economic rehabilitation at the Altro workshop for convalescent patients, has been of inestimable value to the patient. The social worker at the sanatorium has an opportunity indirectly to affect an educational program at the sanatorium for the patient through the rehabilitation worker and occupational therapist, if not through arrangement of reading courses or correspondence courses. With several foreign patients, opportunities were given them to study English under members of the staff or other ambulant patients.

Since the delivery of this paper, a rehabilitation department has been established at Montefiore Sanatorium under the supervision of a man trained in rehabilitation techniques, including vocational guidance, adult education and personal counseling. This has greatly enhanced the possibilities of education at the sanatorium for individual patients as well as providing additional tools of therapy in emotional problems. The social worker's emphasis in vocational education is, therefore, now somewhat changed. She is no longer the instrument through which guidance, correspondence courses, classes and special reading are arranged, but rather plays a supportive rôle. She helps in the selection of patients. She provides background information and case history about patients so that education may relate to the family situation and plans. The social worker also arranges for follow-up after discharge so that there may be continuity of service in the rehabilitation program. She may influence the educational process, by carrying on a treatment relationship with a disturbed patient for whom the rehabilitation director therapeutically arranges placement in a stenography class, after study of his aptitudes for work. The patient has thus gained immeasureably in his opportunities for return to normal, well-adjusted living.

Arrangement for such education is essential for a patient needing to satisfy a wish for recognition or new experience through achievement. It helps to mitigate the destructive features of tedious bed-rest and limited activity over a long period of time. It also can either shorten the training period later, or make up for years out of work, even as a leave of absence for study.

The sanatorium social worker is also able to interpret to the patient the service of the social agencies in the city, such as the Home Relief, child placing agencies and family welfare societies, describing how they are caring for the patient's family in the city. The patient thus may feel comforted, in knowing the facts. Because of recurrent fears and guilt feelings regarding responsibility for his family, this must often be repeated many times over.

The social worker also sees to it that the patient is reinstructed when he begins to return home on passes with regard to precautions, sleeping and eating arrangements, the necessity for rest and his relations with the rest of his family.

But it is at discharge that we see all patients most intensively because then the problem appears more acute. We often discover then that earlier attention to this man's particular problems might have saved energy later. Preparation includes review and reëmphasis of precautions by asking the patient his plans for continuing care. He is told of the resources in the community, the necessity for medical follow-up and, if he cannot afford a private physician, to what clinic he is to report and when. The doctor's recommendations are discussed with him and he is furthermore told of our service for reëxamination for work capacity and possible admission to the Altro or other form of rehabilitation. The procedures as to finding a room, obtaining relief and the other services necessary are reviewed. He is finally on discharge referred back to his district worker, who has prepared the family for his return.

What about our custodial patient? I think the hospital social worker can speak with more authority about him. But he, too, needs education if our function with him is to be fulfilled. That is, to make him as useful and contented a person as possible for his own sake, as well as for the other patients' sakes. Any of the aforementioned methods can come into use here as long as we try to meet the fundamental needs for security, response, recognition and new experience in some way.

So we see that ordinary educational methods are not enough here. The nature of tuberculosis and its cure imply some emotional disturbances in

the patient varying with the objective situation and the original personality make-up of the patient. That is why we must make a thorough study of both. It is a commonplace that we cannot teach those who do not want to learn. Our disturbed patient is often not emotionally ready to learn at first, regardless of what he says. Education here cannot be imposition of certain information and principles upon one person by another, but is a continuous long time process, a relationship, leading to a new orientation to the objective situation.

Regardless of whether the services in a sanatorium are a good deal more limited than described, the same understanding of the patients is necessary and the same fundamentals hold true. The service to the patient will be on a more restricted basis, but none the less valuable.

The tendency is for each staff member to focus on one particular aspect of the patient. But we must all spread ourselves out. He cannot be adequately served as a medical problem, nor as an intellectual problem, nor as an emotional one. He is first and foremost an individual. We must all consider him from that point of view.

BOOKS

EMILE SERGENT: *Suppurations. Bronchiques, Pulmonaires, Pleurales and Mediastinales. Pp. 312, with 78 figures, Masson and Cie., Editeurs, Paris, 1940, paper.*

By H. WESSLER

During the past two decades the study of suppurative diseases of the intrathoracic organs has made tremendous strides. Everywhere clinicians equipped with diagnostic instruments of precision in the use of which they have aetained great skill, have applied themselves with ardor to the diagnosis of these conditions. They have also evolved new methods of treatment in which the surgeon takes an ever greater and successful part. After such a period of rapid progress it is not only desirable but necessary that we take stock of our progress and critically appraise our new knowledge. The excellent monograph of E. Sergent which is herewith reviewed is therefore particularly welcome and timely because it summarizes the experience of France's most distinguished chest physician and those associated with him, and because it speaks with the authority and clinical judgment which is the outgrowth of a vast experience.

This work, a volume of three hundred odd pages, is introduced by a discussion of the fundamentals of diagnosis. This has the merit of focusing attention on essential rather than academic or didactic features of thoracic diseases. Because of their importance much attention is devoted to the subject of pulmonary cavities and also of the characteristics of the sputum in various suppurative conditions of the bronchi and lungs. The author thoroughly recognizes the clinical implications of the foul odor of the sputum with respect to putrid infections of the lung and observes the distinction between the foetor of bronchiectasis and lung abscess. The discussion of cavities is illuminating, although in the use of the term "vomica" the author includes cavities in the pleura, or subphrenic space, which may be confusing to the American reader. However, in thus expressing himself the author recognizes the significance of collections of pus in these locations which, by rupture into and evacuation through a bronchus, may simulate true pulmonary cavities.

Considerable space is devoted to the technique of bronchography and its interpretation and much may be learned from the scholarly and conservative presentation of this subject to which the author and his collaborators have contributed so much.

The main portion of the work pictures in bold outline the major forms of suppuration of the bronchi, lungs and pleura. A considerable part is concerned with the various types of bronchiectatic disease in which, on every page, there is evidence of the profound insight and experience of the author. On controversial questions he expresses his opinions definitely though with moderation. For example, he doubts the congenital nature of bronchiectatic disease and supports his views convincingly by his observations on the developments of this condition in a previously normal lung. The various theories as to the mechanism by which bronchi are dilated are learnedly discussed and the various factors, such as primary damage to the bronchial wall, progressive pulmonary induration and pleural changes are given their just due. The author particularly recognizes the importance of suppurative bronchopneumonia in the causation of bronchiectasis. In this connection also the influence of foreign bodies, tuberculosis and syphilis is emphasized. A strange omission is the failure to mention benign bronchial tumors, such as adenomas which, because of their chronicity, are so apt to cause dilatation of the bronchi.

In the section devoted to the treatment of bronchiectasis the author manifests refreshing skepticism with respect to the time honored methods of treatment. He brushes aside almost with impatience the medicinal and mechanical treatments in which physicians still indulge themselves which have been found so useless. In bronchoscopic irrigations Sergent sees only a palliative measure which decreases stasis and thus diminishes the offensive odor of the sputum due to secondary infection by anaërobic bacteria. He discards pneumothorax as useless because adhesions nearly always prevent a useful collapse of the lung. Although, in general, this view may be regarded as correct, the reviewer is prompted to point out that the suppurative process in the bronchi may be brought to an end by pneumothorax in a small percentage of cases which have not been in existence too long. One can, however, confirm the view of Sergent that even in such cases the dilatation of the bronchi is permanent. He concludes after a critical review of all these methods of treatment that the only definitive cure for bronchiectasis is the surgical removal of the affected lung. He adds a salutory injunction to those who too lightly embark on lobectomy, that they first assure themselves by careful lipiodol injection of the other bronchi that the disease is truly limited to the lobe which they propose to excise.

The author devotes the greatest space to the various suppurations of the lung itself. The American reader will profit greatly from a study of this portion of the work. In respect to pathogenesis, pathology and clinical diagnosis it exhibits a comprehension of the subject which cannot be found in any contemporary publication. The author understands and clearly depicts the profound difference between ordinary pyogenic infections of the lung and those which are characterized by gangrene and he draws the proper conclusions from this difference in respect to treatment. Perhaps too great an emphasis is

placed on the Vincent organism in anaërobic infection of the lung and highly theoretical views are expressed with regard to the various anaërobic bacteria and their relation to the different pathological phases of the disease. But these are minor faults, if faults they are. We must be grateful to the author for his emphasis on the progressive and incurable character of putrid abscess of the lung which, if not promptly eradicated, brings in its train the complications which make its treatment in the chronic stage so hopeless. The not uncommon association of tuberculosis with lung abscess has been a subject of intensive study by Sergent who devotes considerable space to an analysis of this interesting association of diseases.

The treatment of lung abscess is the subject of a constantly recurring conflict between medical and surgical opinion. In this conflict Sergent ranges himself definitely on the side of the surgeon. He freely concedes that putrid abscess of the lung may heal spontaneously and his figure of 20 per cent of such healing is in accordance with the experience of physicians in this country. He therefore believes that patients may be encouraged for several months to hope for such a spontaneous cure. Failing this, they should have their abscesses drained surgically. Such drainage brings about a definitive cure in a large percentage of the cases. The author performs this operation in two stages during the first of which he incites a local pleural reaction in order to ward off the operative area. Because of the serious and often fatal result of pleural infection by anaërobic bacteria the author may be pardoned for this precaution. However, it may be observed that such two-stage operations have been found unnecessary in this country by surgeons who have had great experience in the treatment of putrid lung abscess. It is well known that the pleura in the immediate vicinity of a lung abscess is almost invariably adherent and that with proper localization the abscess may be directly incised without preliminary treatment of the pleura.

The final part of this work is devoted to the subject of suppuration in the pleural cavity and in the mediastinum. It will surprise the American reader that Sergent finds it necessary to combat a considerable body of opinion in his country which favors the purely medical treatment of empyema, especially the frequent aspiration of the purulent effusion with or without chemotherapy. It is hardly necessary to state that Sergent thrusts such consideration aside and firmly states that the treatment of empyema is operative. On the other hand the reader may be permitted some skepticism over the optimistic expressions of the author in regard to the medical treatment of tuberculous empyema. To quote the author: "The treatment of tuberculous pleural effusions must above all be sought in the method of successive aspirations followed by reinsufflation of air or by the injection of modifying substances" (Gomenol). Operation is reserved for cases of secondary infections of the pleura or other exceptional conditions. The American reader with experience

in the treatment of tuberculous empyema may doubt that a considerable number of cases can be brought to cure by this means.

The reader who seeks an exhaustive and didactic exposition of suppurative diseases of the chest may be disappointed by some omissions and by a lack of reference to work in this field in other countries than France. There are only casual references to the contributions made by Americans and by the English. The reader must, however, bear in mind that this work represents the personal observations of Sergent and his coworkers which have been crystallized into well tested views over a period of years. Though not specifically acknowledged, we may assume that there is implicit in this work whatever there may be of value in the labors of others in this field. Viewed in this light it must be regarded as one of the most outstanding contributions to the subject of intrathoracic suppuration.

R. A. McCance and E. M. Widdowson: *The Chemical Composition of Foods. Pp. 150 with numerous tables, Medical Research Council, London, His Majesty's Stationery Office, 1940, fabrikoid.*

By LENNA F. COOPER

The Medical Research Council of Great Britain has for a number of years sponsored the investigation of McCance and Widdowson, the report of which is now published and constitutes the most complete analysis of British foods yet published. One section of the book is devoted to "Composition Per 100 Grammes" and another section to "Composition Per Ounce." Cooked foods are included, as well as raw. Several pages of recipes appear, upon which the analyses of the cooked foods are based.

As in several previous publications by the authors, the work is based upon the "available" factors. Available carbohydrate is given as "the sum of the starch and dextrins (expressed as glucose) and sugar. For the calculation of calories the factors 4·1, 9·3 and 4·1 have been used for protein, fat and carbohydrate, respectively." "Available" phosphorus (other than phytic acid) is given, as well as "available" iron.

Because of the use of the available factors, about which there is some difference of opinion, the figures vary considerably from the analyses of American foods, especially for those of the fruits and vegetables.

The analyses include not only water, sugar, starch, available and unavailable carbohydrate, total nitrogen, protein, purine nitrogen, fat and calories, but also nine of the most important mineral elements, likewise, the acid-base balance. The data on mineral composition make the book especially valuable. Since as many as twenty different constituents had to be determined for many

of the foods analyzed, one can well appreciate the tremendous task that has been accomplished by the authors.

LEWIS J. MOORMAN: *Tuberculosis and Genius. Pp. xxxv + 272 with 11 photographs, The University of Chicago Press, Chicago, 1940, cloth, $2.50.*

By MAX PINNER

The association of tuberculosis and genius has given rise to many a facile essay and some thoughtful treatises—and the question still remains unsolved what rôle, if any, tuberculosis has played in the shaping of genius. The unrealistic and romantic mind cannot but see in the tragic limitation of the tuberculous, in his early doom and in his relentless but futile fight against the consuming disease, in his restrictions that so easily lead to paranoic trends—or poetically seen—to unwordly aloofness, factors that make up some of the minor and more theatrical facettes of genius. But more realistic studies in which the premorbid personality was compared with that modified by disease, tend to show that tuberculosis is *per se* no creator of greatness. Tuberculosis, so frequent a disease, particularly one or two centuries ago, probably strikes impartially the great and the common-place person, leaving on each its stamp, possibly emphasizing premorbid characteristics, such as concentration, strength of purpose and an indomitable spirit. It throws the individual on his own inner resources for the greater use of them—if they are valid, and it leaves the patient without such resources, the utter hollow crank with an asocial behavior pattern. But still, if one reads again the biographical sketches presented by Doctor Moorman, one wonders whether tuberculosis has not added intensity and the inner burning fire to these lives. In Doctor Moorman's competent and sympathetic biographies, certainly admiration and compassion are aroused. One characteristic is particularly striking, as pointed out again and again by the author (and as seen in the humblest and mentally most insignificant of our patients) and this is the *spec phthisica*, the ever returning hope, the unwarranted optimism. This is probably the one characteristic which strikingly belongs to tuberculosis more than to any other chronic disease. Doctor Moorman again questions in his thoughtful introduction whether this hope is a specific biological factor in tuberculosis, whether there is something in the chemistry of the bacillus or the disease that causes it. It seems to me—and many expatients have agreed with me—that one plausible explanation derives from the exacerbations and remissions that are such a characteristic feature of the disease. In each exacerbation, past remissions are remembered—the source of hope and reassurance.

Doctor Moorman presents eleven biographical essays, an interesting selec-

tion of the great who were tuberculous. They make good and interesting reading. While the episodes of disease, its stimulation and its paralyzing and limiting effects, are always emphasized, one would wish to know more intimately the rôle that the disease has played. But the records are incomplete, beyond the grasp of any biographer. Doctor Moorman wisely refrains from deciding whether each of these eleven persons was a genius because he had the disease or in spite of it. Probably, he leans toward the second alternative. And this gives to this book its real significance; it shows how in spite of fever, fatigue and all sorts of physical suffering, there was accomplishment and greatness and cheer. It shows—here or there—not only the heroic victory over disease, but the astounding adaptation that man is able to make to disease. For this reason, first of all, should Doctor Moorman's book reach many patients and many physicians. It will help patients to carry their burden with patience and hope, it will convince them that even a brief life, complicated by disease, need not exclude the possibility of accomplishment; and it will teach physicians a deeper sympathy and understanding for their charges. It may even show some of the young and all too healthy physicians that many of the behavior difficulties of tuberculous patients are not primarily to be viewed as ingratitude and violation of discipline but as immanent symptoms of the disease. For all these reasons Doctor Moorman's book will fill an important function; it certainly belongs in the patients' library of every tuberculosis ward.

Savoir Prevenir. Edited by Lucien Viborel. Pp. 317, Paris, 1939, paper.

By LOUIS E. SILTZBACH

This paper-bound book is one of the last to come out of peace-time France. It is an admirably concise survey of the state of preventive medicine in that country and of the progress made in this branch of medicine up to and including last year.

The editor has gathered together outstanding medical authorities in the numerous fields of preventive medicine and in twenty-one brief chapters each writer has outlined the principles underlying the organized activities in maternal welfare, infant hygiene, sanitation, nutrition, mental disease and the fight against cancer, tuberculosis, venereal disease, diphtheria, *etc.* The essays are sprinkled with pertinent statistics on the degree of success attained in each of these fields. At the end of each chapter there are appended complete lists of the names and locations of the stations and institutions which are carrying out the work discussed. The hospitals, clinics, public health offices and welfare agencies are listed geographically—an excellent compilation for ready reference.

The chapter on the antituberculosis campaign in France is written by Professors R. Debré, Etienne Bernard and J. B. Evrot. It sets forth the now generally recognized principles underlying the fight against tuberculosis. France has shared in the universal decline of the tuberculosis death-rate which has occurred in the past few decades. However, the last figures quoted, those for 1934, showed 128 deaths per 100,000 population, a rate considerably higher than that for the United States, Holland, and Denmark, which was approximately 50, and higher than that for England and Germany, which was approximately 75 per hundred thousand. Of particular interest are the statistics on BCG vaccination in France. These had risen from 4,328 infants vaccinated; *i.e.*, 0.56 per cent of the total annual births in 1925, to 210,668, or 32.9 per cent, of the total annual births in 1935. The innocuousness and effectiveness of the procedure are defended by the authors.

This book, published just before the outbreak of the war, takes on historic value in the light of subsequent events. To what extent has the military occupation of France altered the picture of preventive medicine which is presented in this book? A sequel to this survey, by future medical historians, will tell us.

VICENTE E. DE PABLO: *La Arquitectura Bronchopulmonar. Pp. 63, illustrated, A. Guidi Buffarini, Buenos Aires, Argentina, 1940, paper.*

By ESMOND R. LONG

In this monograph the author presents a study of bronchial architecture based on plastic injections of formalin-fixed human lungs, dissections of pulmonary lobules and numerous bronchographic X-ray film examinations. The volume is divided into three parts, dealing respectively with anatomical classification of the bronchi and their divisions, a dissectional and injectional study of the pulmonary lobules and, finally, a section on bronchopulmonary segments. The anatomical classification of bronchial divisions is meticulous, and the reader will find the accompanying diagrams useful for precise descriptive localization. The chapter on pulmonary lobules is written in the light of well known studies, including those of W. S. Miller, Loeschke, Husten, Aschoff and Grethmann. De Pablo disagrees with certain phases of the classification of most of these authors, for example, Miller's postulation of a "vestibule" and an "atrium." His conclusions are based largely on his injection casts, the photographs of some of which are impressive, although they would be more convincing if published with greater magnification. The technique for the injection is given. The final section of the monograph carries a series of rough drawings of the character of segments of the lung or sublobules, as they

vary according to location, and of different planes of the two lungs. In general the reader will find the monograph very useful for accuracy in anatomical description.

ARMANDO SARNO, RAUL A. PIAGGIO BLANCO AND ALEJANDRO ARTAGAVEYTIA: *Las Meningitis Tuberculosas del Adulto. Pp. 312. illustrated, El Siglo Ilustrado, Montevideo, Uruguay, 1940, paper.*

By ESMOND R. LONG

In this book the authors analyze in the light of a well considered review of the literature their experience with forty-nine cases of tuberculous meningitis. Chapters are devoted to the relation between meningitis and the character or stage of tuberculosis existing elsewhere in the body, the pathological anatomy of the disease, its clinical course, the characteristics of the cerebrospinal fluid, diagnosis, prognosis and treatment. In consideration of the relation between meningitic process and stage of tuberculous infection elsewhere in the body the authors point out that tuberculosis in Uruguay is somewhat distinctive in its relatively high proportion of cases of primary disease in adolescent or adult life. The Ranke concept of evolution of tuberculosis is followed, without overly rigid adherence to the systematization in this concept. The chapter devoted to clinical course is most significant, because of the authors' attempt to classify their thirty-three best studied cases with regard to origin. Seven cases were believed to have developed within the primary phase of tuberculosis, four to be early in the postprimary pulmonary stage, ten to be the result of haematogenous spread from an extrapulmonary focus and twelve to be sequelae of well developed reinfection-type pulmonary tuberculosis. The evidence for the truly primary nature of the four first cases in this list is unconvincing, particularly as, for the most part, it was clinical only, but it is clear from the record that tuberculous meningitis as a part of primary tuberculosis in the adult is relatively rare. The preponderance of cases were obviously derived from well developed visceral or chronic pulmonary tuberculosis. In only twelve of the forty-nine cases was necropsy performed, a number too small for serious consideration in comparison with the many extended pathological anatomical studies on record. The authors' conclusions, however, are conservative and unbiased. The book is valuable for its thorough consideration of the abundant literature on the subject and its practical consideration of a series of personal observations in the light of the divergent views in the literature.

Books Received

INJO BENG LIONG: De Tuberculine Reactie. Pp. 203 with many tables and graphs, Keng Po, Batavia, 1940, paper.

Your Health. A Guide to the Medicine and Public Health Building, New York World's Fair, 1940. Pp. 96 with many illustrations, American Museum of Health, New York City, paper.

MANOEL DE ABREU AND ALOYSIO DE PAULA: Roentgenfotographia. Pp. 185 with 123 illustrations and many tables, Livraria Ateneu, Rio, 1940, paper.

E. V. MCCOLLUM AND J. ERNESTINE BECKER: Food, Nutrition and Health. Fifth edition, pp. v. + 127, McCollum and Becker, Baltimore, 1940, cloth, $1.50.

Memoria del Primer Congresso Venezolano de la Tuberculosis, celebrado en la Cuidad del 8 al 11 de Diciembre de 1938, pro la Sociedad de Tisiología de Venezuela. Pp. 576, with charts and figures, Venezuela, 1938, paper.

RALPH H. MAJOR: Physical Diagnosis. Second edition, pp. XIV + 464, with 437 illustrations, W. B. Saunders Company, 1940, cloth.

WILLIAM H. HOLMES: Bacillary and Rickettsial Infections, Acute and Chronic. Black Death to White Plague. Pp. vii + 676, Macmillan Company, 1940, cloth, $6.00.

EUGENE DE SAVITSCH: In Search of Complications. Pp. 396, Macmillan Company, New York, 1940, cloth, $3.00.

TUBERCULOUS CAVITIES[1, 2]

Observations on Transpleural Decompression

ALFRED GOLDMAN, HAROLD BRUNN AND LAUREN ACKERMAN

In 1935, Semb (1) wrote, "The so-called 'collapse therapy' in pulmonary tuberculosis, the artificial pneumothorax, packing, thoracoplasty, phrenicectomy, *etc.*, developed on empiric basis. . . . The theoretical conception of its effect on the tuberculous process is still under discussion." Collapse therapy is largely cavity therapy. Many cavities have failed to close after compression therapy, and often the results of a surgical form of compression have been unpredictable. Studies of the behavior of cavities during transpleural decompression (modified Monaldi method (2)) gave us clinical and experimental observations for certain general concepts of cavities. The purpose of this paper is to present these and other observations of cavitation made during the past three years, which have served as the basis for our concepts of the origin, maintenance and disappearance of cavities.

The material and methods on which we base our concepts include the usual clinical material found in a tuberculosis hospital of 200 beds,[3] studied particularly for bronchial disease; approximately 350 bronchoscopic observations; a series of approximately 100 postmortem examinations especially for bronchus-cavity valves; 73 patients treated with thoracoplasty and 20 cavities treated with transpleural decompression. Intracavitary pressure changes, normally present or artificially induced in these cavities, were studied by means of a recording kymograph. Cavernoscopic examinations were made of 7 cavities. Bacteriological examinations were made of the drainage from the cavities at frequent intervals. Frequent roentgenograms and repeated cavernographic studies were used as a final check of the disappearance of the cavity

[1] From the Department of Thoracic Surgery, University of California Medical School and the Tuberculosis Division of San Francisco City and County Hospital, University of California Service, and the Department of Public Health, Dr. J. C. Geiger, Director; aided by a grant from the Lilly Spreckels Wegeforth Fund.

[2] Read at a meeting of the American College of Chest Physicians, New York City, June, 1940.

[3] University of California Service at the San Francisco Hospital.

being treated by transpleural decompression, and also to demonstrate the existence and nature of its bronchial communication (plates 1 to 9).

POSTMORTEM FINDINGS

At every autopsy the draining bronchus of the cavity was grossly affected. Some very large cavities with cavity walls of compressed and scarred lung adherent to the parietal pleura had a single, large, patent bronchus (figure 1). Others associated with marked caseation had trabeculae traversing the cavity. The draining bronchi took many forms and shapes. Near or in the cavity walls, morphological changes were found in the bronchi which might, under certain poorly understood conditions, produce one-way valvular arrangements allowing air to flow predominantly in the direction from bronchus to cavity. These changes were descriptively termed check-valve, accordion valve, by-pass valve and flutter-valve (figure 2), according to their form. Complete obstruction of bronchi was also seen. In addition, it was realized that any secretions, such as a single drop of fibrinous exudate in the bronchus-cavity opening or a pool of liquid secretions lying in the cavity over a narrow bronchial opening, might readily produce one-way valves controlling air-flow predominantly in the bronchus-to-cavity direction. The physiological effect of these bronchial valves is to entrap air in the cavity, and thus produce a greater tension than is present in the surrounding lung. For these reasons, we might expect some of these cavities treated with artificial pneumothorax to rupture through the pleura (figure 3).

CAVERNOSCOPIC FINDINGS

In some cavities, by cavernoscopic examinations during transpleural decompression, we (Coryllos (3)) have seen air enter cavities through a

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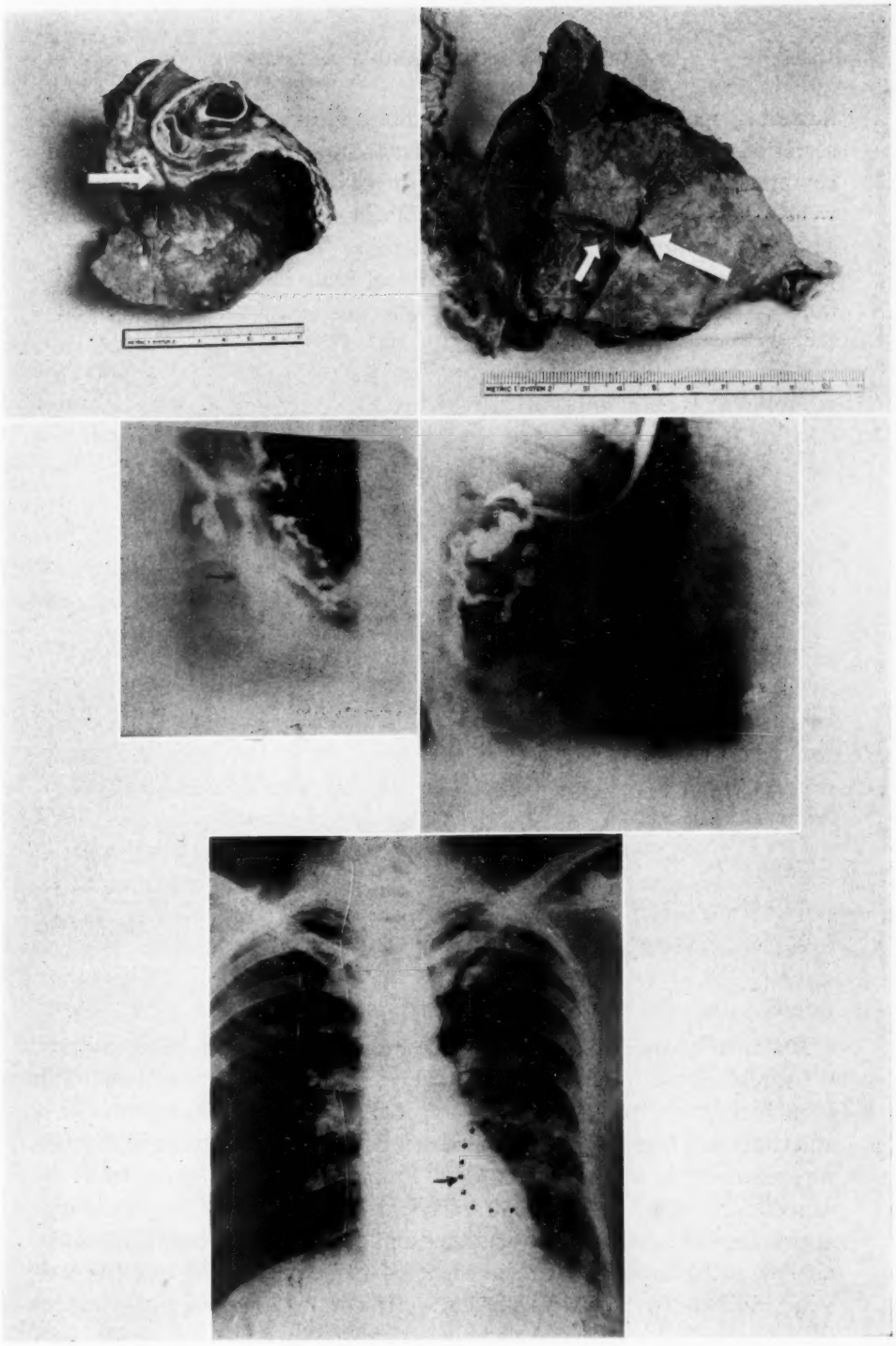
FIG. 1 (upper left). E. L. 10/25/38. Postmortem specimen of large cavity showing scarred walls with extensive pleural adhesions. Only one tortuous, narrowed bronchus entered the cavity.

FIG. 3 (upper right). M. J. M. Postmortem specimen of a small tension cavity ruptured into the pleura during reëxpansion of the lung three years after artificial pneumothorax. Small arrow points to the bronchus-cavity opening; the large one to the rupture of cavity at the pleura.

FIGS. 4 (center left) and 5 (center right). J. C. 10/10/38. Posteroanterior and left lateral spot films after serial bronchography. Arrow points to the remains of a large, circular cavity in the left lower lobe (figure 6). Sputum negative for three years following permanent paralysis of the diaphragm. Bronchoscopy showed bronchial stenosis.

FIG. 6 (bottom). J. C. 12/21/34. Roentgenogram showing a large cavity with a fluid level in the left lower lobe.



FIGS. 1, 3, 4, 5, 6.

fluttering spot or have even seen bubbles rising from pools of liquid secretion at the bottom. Serial cavernoscopy during transpleural decompression has disclosed changes in the cavitary walls. Within a few weeks they lost their shaggy, yellow, fibrinous appearance and became smooth and pink. The secretions at times became less fibrinous and purulent until they were clear and serous, lying in a pool in the cavity depth, or stayed purulent until the tube was removed.

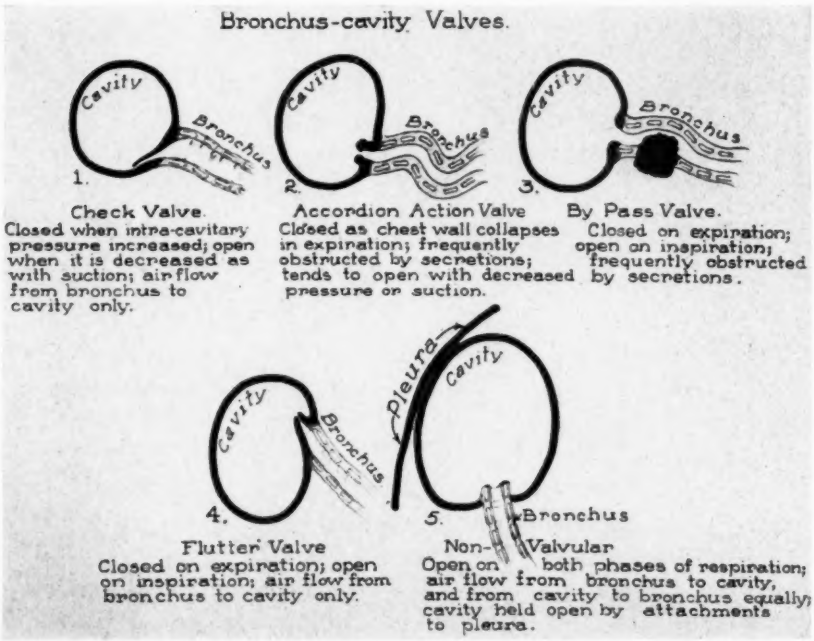

Bronchus-cavity Valves.
Cavity
Bronchus
1.
Check Valve.
Closed when intra-cavitary pressure increased; open when it is decreased as with suction; air flow from bronchus to cavity only.
2.
Accordion Action Valve
Closed as chest wall collapses in expiration; frequently obstructed by secretions; tends to open with decreased pressure or suction.
3.
By Pass Valve.
Closed on expiration; open on inspiration; frequently obstructed by secretions.
4.
Flutter Valve
Closed on expiration; open on inspiration; air flow from bronchus to cavity only.
Pleura
5.
Non-Valvular
Open on both phases of respiration; air flow from bronchus to cavity, and from cavity to bronchus equally; cavity held open by attachments to pleura.

FIG. 2

If similar changes took place in the walls of bronchi draining cavities, we would expect more patent bronchi with less efficient valves. The bronchial lumen would be less obstructed as its walls became smoother and contained less secretions. Evidence of reversible histological changes was observed in some bronchi (4). From their nature, they would be expected to revert to bronchial valves of less efficiency. With the disappearance of inflammatory exudates and oedema of the bronchial walls, air-flow along bronchi could be expected to be obstructed less and valvular mechanisms to be less efficient. However, the histological changes in the bronchial walls were not always reversible and more or less per-

manent valve mechanisms were formed. Besides bronchial changes which allowed some air-flow, even though less than normal, other occlusive changes completely obstructed the lumina both temporarily and permanently.

Bronchoscopic observations disclosed some evidence of involvement in about one-third of the cases. Simple oedema and haemorrhagic injection were most common. Tubercles, polypi, ulcers and hard and soft localized stenoses were less common. These observed bronchial lesions were only the visible tips of invisible processes in more distant bronchi, that is, in bronchi nearer to cavities. We observed frequent involvement of bronchoscopically invisible bronchi in histological sections and gross dissections of postmortem material. Additional clinical observations offered further evidence of not only the presence of bronchial disease where it could not be bronchoscopically visualized, but also of its rôle in the behavior of cavities, both treated and nontreated.

BRONCHOGRAPHY

These further observations just alluded to were made by serial bronchography (figures 4 and 5) and serial cavernography (plates 1 to 9). Serial bronchograms of the bronchi distal to areas of stenosis showed elongated, single or multiple, narrowed, tortuous channels, the remnants of diseased bronchi, draining areas of or near former cavitation (figures 4, 5 and 6). After artificial pneumothorax, less complete bronchial obstruction was demonstrated than after thoracoplasty.

In the bronchi supplying the lung surrounding cavity, both bronchiectasis and complete bronchial obstruction occurred. Following thoracoplasty, lobar obstruction and obstruction of smaller bronchi were observed.

When bronchi could be outlined leading to cavities not responding to thoracoplasty, they were usually narrowed and tortuous. Cavernograms disclosed tortuous, narrowed bronchi draining tiny or large residual cavities after thoracoplasty, extrapleural pneumothorax and transpleural decompression (plates 1 to 9). In some cases, complete bronchial obstruction was demonstrated (C. T., plate 2).

Roentgenological observations were made of atelectasis (5) and the apparent relation to certain cavities. At times after pneumothorax, sudden occurrence of atelectasis was associated with the appearance and increased prominence of cavities not previously visible (7). On the other hand, we found the disappearance of cavities to occur simultane-

ously with the disappearance of neighboring atelectasis. Artificial pneumothorax frequently produced atelectasis without disappearance of the adjacent or central cavity, but when the pneumothorax was allowed to diminish, the cavity also disappeared. Associated with these former occurrences of atelectasis, evidence of bronchial disease was always observed and demonstrated (6). In many instances, the bronchial disease with or without atelectasis could be demonstrated when no cavity existed. In some cases, temporary bronchial obstruction producing alternating atelectasis and aëration became permanent bronchial obstruction and atelectasis, with or without demonstrable cavity within or near the atelectasis.

Reversible bronchial obstruction producing atelectasis, such as that frequently associated with artificial pneumothorax, may be relieved by abandoning the compression therapy, and so producing reaëration of the atelectatic lung (8). We have seen 14 cavities more prominent during artificial pneumothorax disappear with the disappearance of the pneumothorax. But more often, abandoning of artificial pneumothorax was accompanied by no change in atelectasis or cavitation. Another clinical observation which is entirely related to alterations of bronchus-cavity mechanisms, is the sudden disappearance and reappearance of solitary round cavities with thin walls of increased density (9).

From our observations, it appears that atelectasis has no constant relation with the appearance, maintenance or disappearance of cavities. The evidence at hand points to the aetiology of the pathological changes which result in both atelectasis and in cavity as having the same underlying basis, namely, bronchial tuberculosis. That on the one hand atelectasis is produced, and on the other cavitation, is probably related to the different types of bronchial tuberculosis and to their different locations. For example, we would expect a bronchial change near a soft caseous area which acts to entrap air distally to bring about a cavity. Conversely, a complete obstruction of a lobar bronchus without distal entrapping of air would produce a lobar atelectasis without cavitation.

INTRACAVITARY PRESSURE

The measurements of pressure changes in cavities is evidence of their behavior. The initial pressures vary with respiratory movements; usually they swing to several centimeters of water on the positive side. These pressure have been studied by means of continuous kymographic recordings in patients undergoing transpleural decompression therapy.

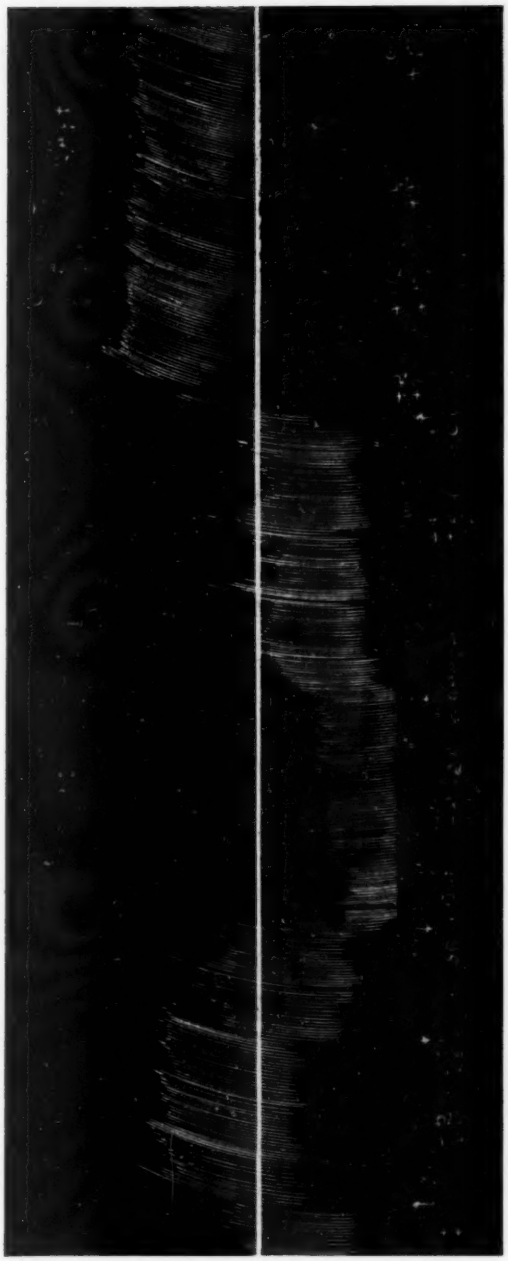


FIG. 7. C. T. 6/15/39. Left. Three weeks after transpleural decompression. Bronchus previously open, as demonstrated with methylene-blue. Kymographic tracings showing effects of artificially elevating pressures within the cavity, and of artificially diminishing pressures within the cavity by injection and withdrawal of air, respectively. Only when the pressures were artificially made more negative did a leakage of air occur within the cavity. This was announced clinically by the presence of audible wheezing, which occurred simultaneously with the increase of pressures from -9, -2.5 to -4, $+2.5$. Elevations of pressures to $+2$ $+7$ produced no evidence of leakage of air out of the cavity.

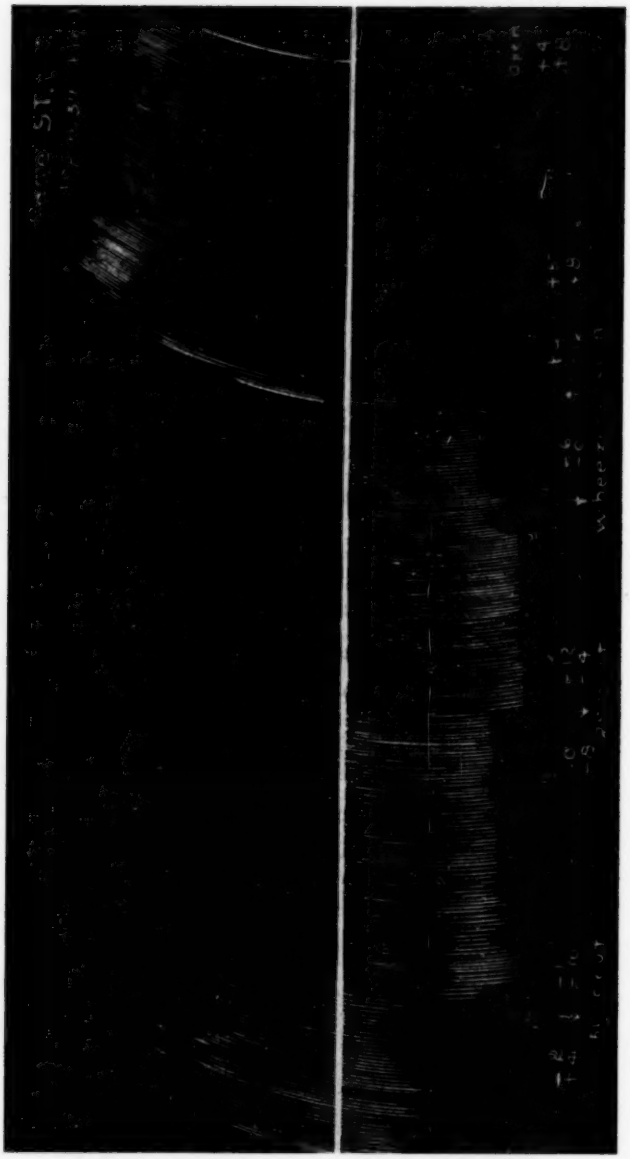


FIG. 8. S. T. 10/16/39. Kymographic tracing of intracavitary pressures made immediately after insertion of metal cannula into the cavity in the right upper lobe. The pressure changes were similar to these demonstrated in figure 8. In this case the pressures were reduced to −12, −4 by removal of a total of 75 cc. of air. Concomitant with the appearance of the wheeze, the pressures rose to −6, 0. This indicated leakage of air into the cavity. But about one minute later, the pressures were artificially raised to +7, +12, after injecting 75 cc. of air into the cavity; and no leakage of air out of the cavity occurred through the bronchi. This demonstrated that the valvular mechanism was one-way, from bronchus to cavity but not from cavity to bronchus.

We observed that changes in the intracavitary pressures were only infrequently related to the actual breathing of the cavity, that is, the actual flowing of air into the cavity with respiration. In tension cavities this

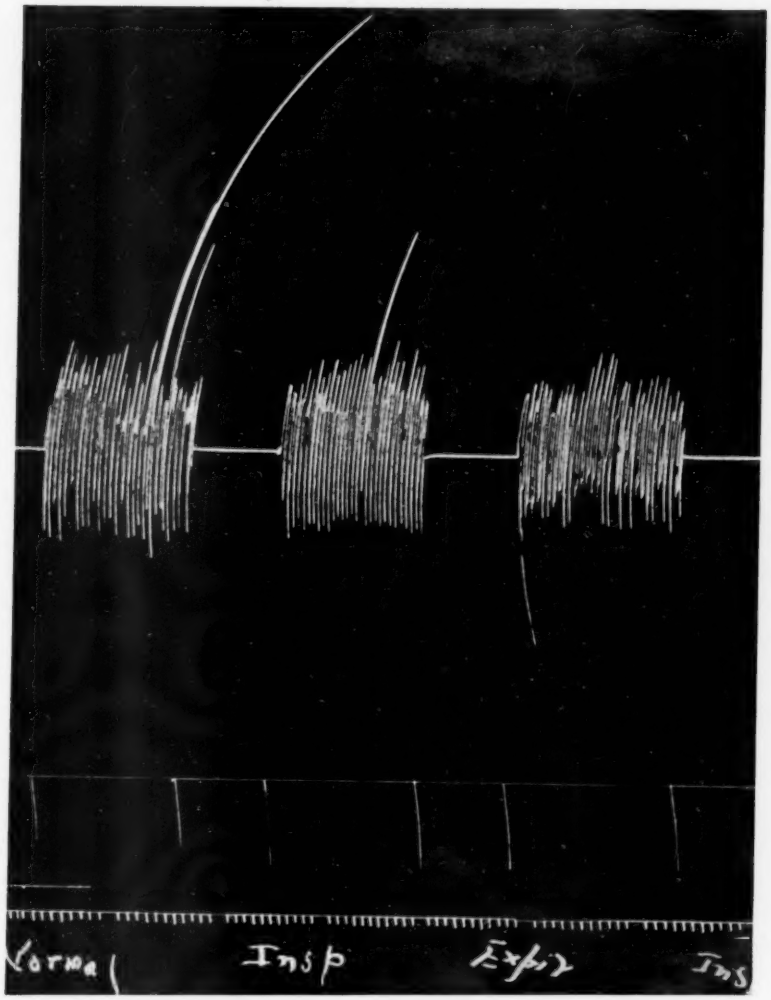


FIG. 9. L. F. (See plates 7, 8 and 9.) Kymographic tracing showing failure to maintain artificial raising or lowering of the intracavitary pressures.

phenomenon seemed to occur rarely during their daily life (figures 7, 8, 9). Calculating the amount of air actually leaking into such a cavity during twenty-four hours would given an answer usually under 10 cc.

in a cavity whose volume was approximately four times this amount. Furthermore, the flow of air from the bronchus into the cavity does not occur bit by bit with each inspiration or expiration, but only occurred at very infrequent periods over the course of a few respirations. The condition under which this leakage of air can be artificially induced occurs when we induce a negative pressure in the cavity by sucking out its air (figures 7 and 8).

That the bronchus-cavity relationship at most times is valvular, with the valve prohibiting the passage of air predominantly from cavity to bronchus, was proved in a number of experiments. Air was introduced transpleurally into the cavity so that the pressures in the cavity were elevated to approximately +18, +24 cm. of water (figure 8). In no instance did a significant decrease of these pressures occur during the periods of our experiments. The efficiency of the valve was 100 per cent, —a complete stop-valve action occurred,— so that no air flowed out of the cavity through the bronchus at the pressures used over a period of from five to thirty minutes, totaling several hours.

In certain cavities, after a period of transpleural decompression, the cavity-bronchus relation showed evidence of change. Thus, in one case which had a stop-valve action early in its course of decompression, an opening had occurred which allowed the pressures to fall when they were artificially raised by the transpleural injection of air. Other cavities containing an open though valvular bronchus-cavity mechanism showed a change of this mechanism so that, instead of acting as an efficient valve, no air at all could be induced to enter the cavity in spite of artificially induced high negative pressures; and cavernograms failed to demonstrate any communicating patent bronchus. In two cavities not closed by thoracoplasty, we obtained pressures that indicated these cavities had a bronchus-valve relationship maintaining the pressures constantly on the positive side and, even after artificially inducing negative pressure within these cavities, the pressure was soon built up again. In one instance the pressures were +2, +12 (figure 10), and in the second, +10, +20.

A type of large cavity was also observed which had a cavity-bronchus relationship incapable of showing highly efficient valvular effects at the times of our experiments; no deviations were ever observed on several attempts during a period of ten months (figure 9 and plate 9). In all the experiments, the artificially induced negative or positive pressures were never maintained for more than one or two respirations. A rela-

tively unobstructed nonvalvular bronchus-cavity relationship was present and was stable and unchanging. This was not a tension cavity, its pressures being nearly that in bronchi, 0, +2.

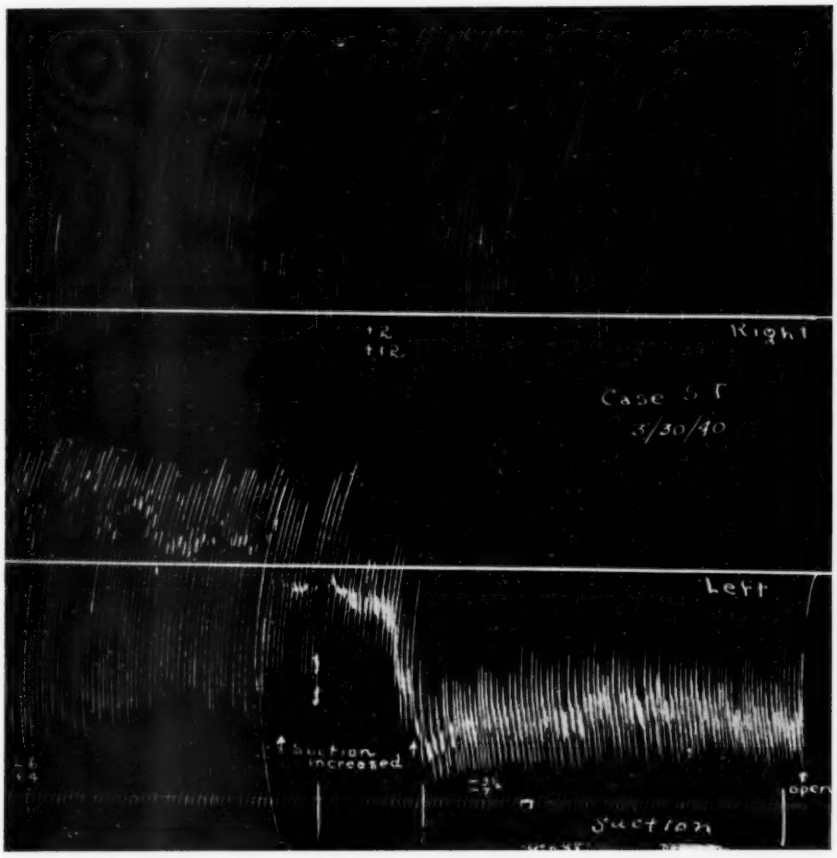


FIG. 10. S. T. 3/30/40 Simultaneous tracings of intracavitary pressure changes in bilateral cavities. The cavity on the right has been under transpleural decompression for five months (plate 5). The cavity on the left has been under transpleural decompression for only a few hours. Patent communicating bronchi have been demonstrated by cavernograms on the right but none on the left (plates 5 and 6). That the bronchus-cavity relationship of the cavity on the right continues to be valvular, is shown by the high pressures maintained in this cavity, positive in both phases of respirations. The effect of suction by motor on the intracavitary pressures is shown in the tracings of the cavity on the left.

Briefly summarizing the findings, we may say that kymographic tracings of intracavitary pressures show that:

1. In tension, or "blocked" cavities, respiratory fluctuations of pres-

sure are caused by the pressures transmitted through the walls of the cavity from their surrounding lung. These fluctuations are greater and higher than in nontension cavities.

2. In tension, or "blocked" cavities, very little actual flow of air in and out of the cavities could be demonstrated.

3. In tension, or "blocked" cavities, the valve formation is usually 100 per cent efficient in the cavity-to-bronchus direction. In these cavities, the pressures may be positive in both phases of respiration (figure 10).

4. Pressure changes consistent with leakage of air into tension cavities were observed when the intracavitary pressures were artificially made highly negative. The valvular efficiency of a cavity-bronchus relationship has been demonstrated to change during the course of transpleural decompression therapy. But terminally, complete obstruction of the draining bronchus may occur (plates 1 to 9).

5. Nontension cavities may have pressures simulating the normal bronchial pressures.

6. Nontension cavities have no demonstrable, highly efficient valve mechanism.

7. Nontension cavities may have a flow of air in and out of the cavity with each respiration.

Our concept for the explanation of the mechanism producing higher pressures within cavities than exist in the surrounding lung, is based on sound principles of physics.

Let A equal the atmospheric gas pressure; P, the intrabronchial pressure and P_1, the intracavitary pressure and S, the pressure in the surrounding lung. A is constant and numerically zero (15 pounds per square inch); P varies with the movements of respiration and, excepting for a slight lag, is equal to S (figure 11).

According to physical laws, air flows in a tube only from a point of higher pressure to a point of lower pressure, therefore, air can only flow into the cavity when P is greater than P_1. This pressure relationship is disturbed when a contiguity of the flow of air is disturbed.

In pulmonary tuberculosis the contiguity of the flow of air is disturbed by bronchial tuberculosis with its accompanying morphological changes producing valvular effects. In both phases of respiration, air tends to be entrapped within the cavity and P_1 may thus become greater than

S or P. The exact phase of respiration during which air flows from P to P_1 occurs when the pressure in P_1 is less than P. Thus, if we artificially reduce the pressure in P_1 so that it is less than P, we can observe pressure effects consistent with the leakage of air to the cavity (figures 7 and 8). In tension cavities, P_1 has been observed to be greater than P. According to physical laws this can only occur if a valvular mechanism exists between P_1 and P. During cough, P becomes much greater than P_1 because of the lag in the development of the high pressure within the cavity. For a short period, conditions may be satisfactory for a

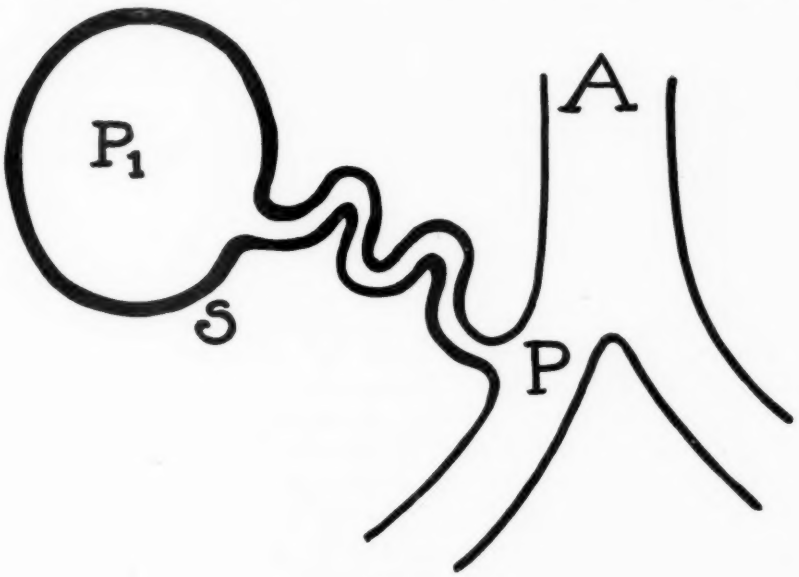


FIG. 11

flow of air from P to P_1. The flow of air from P to P_1 or from P_1 to P will depend to a certain extent upon the nature of the connections between P and P_1, which is conditioned by the nature of the bronchus. The respiratory pressures observed in the graphs did not coincide with the pressure changes connected with leakage of air into or egress of air from the cavity; it can be deduced, then, that the pressure changes within the cavity with respiration are not caused by the flow of air in and out of the cavities. The respiratory changes of pressure are due to transmitted changes from the surrounding lung with the respiratory movements.

TRANSPLEURAL DECOMPRESSION

In all, we have attempted transpleural decompression on 20 cavities in 18 patients (two bilateral cases). In 7 instances, the treatment was not completed, either because of failure of coöperation on the part of the patient, an apparent aggravation of the existing tuberculosis or serious complications such as tension pneumothorax (2 cases).

There were 3 deaths in this series. Both patients who developed tension pneumothorax and empyema died. In both of these cases, preliminary pneumothorax attempts were not adequate; in one instance only one attempt had been made. This led to the development that pneumothorax attempts shall be made in at least five different locations. A third death was caused by tuberculous pericarditis, apparently unrelated to the treatment.

The following reports of cases undergoing transpleural decompression are typical of the course they pursue.

Case 1: E. E. (plate 1), a white female aged forty-one, entered the San Francisco Hospital in 1937 with a cavity in the left upper lobe. Artificial pneumothorax was attempted, but after a few months this was abandoned because of extensive adhesions. Thoracoscopic examination had shown that it would be dangerous to cut the adhesions. In 1939, thoracoplasty was advised but refused and the patient signed her release. After a few months she reëntered on August 28, 1939 with a recent exacerbation of fever, cough and sputum. In September, bronchoscopy failed to show any definite stenosis. Pneumothorax was again attempted at five points over the right upper chest but no space could be obtained. Sputum was 2 ounces, weight was stationary and there was mild fever occasionally in December, 1939. Cough was paroxysmal and very disturbing.

On January 5, 1940, X-ray films of the chest showed that the cavity had enlarged, and infiltrations were present in the left lung and in the right upper lobe (plate 1-A). Initial intracavitary pressures read on a water manometer January 30, 1940 varied from -1, $+0.5$, to -2, $+8$. The high pressures were not always maintained. A valvular action from bronchus to cavity was thought to exist, although it was not 100 per cent efficient. A number 12 French rubber urethral catheter was inserted into the cavity in the first interspace at the mid-clavicular line at this time and transpleural decompression was started. Aspirated secretions contained large numbers of acid-fast organisms and very few formed pus cells. Wangensteen suction was started forty-eight hours later. Within twenty-four hours, the sputum had decreased and the cough had stopped. On February 11, twelve days after the start of the transpleural decompression, 2 ounces daily of purulent, slightly

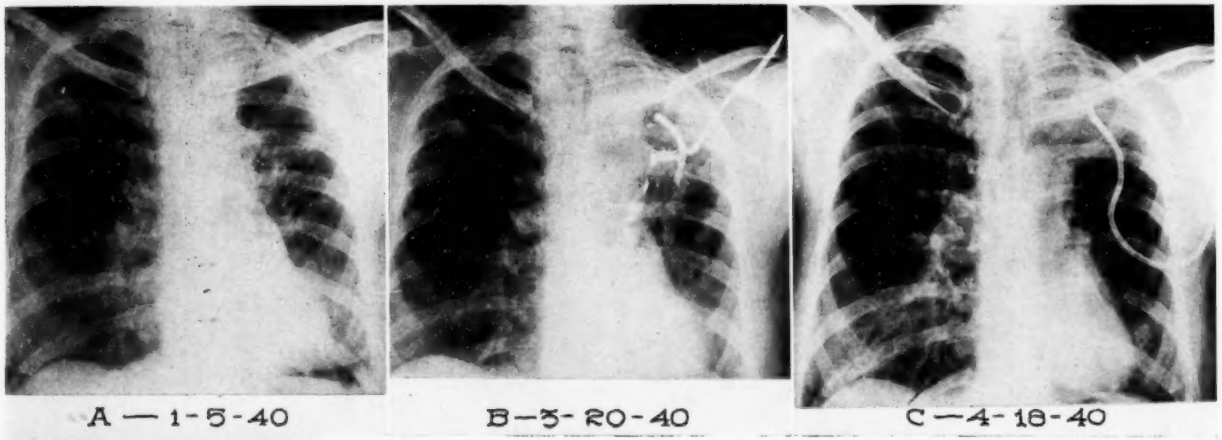


PLATE 1

TRANSPLEURAL DECOMPRESSION (TPD)

E. E., W. female, age 41.

A. Large cavity L.U.L. Pressures—2 + 8. Positive for T.B.

B. 7 weeks after TPD. Cavernography; cavity smaller, bronchus open. Secretions negative for T.B. for 2 weeks.

C. 10 weeks after TPD. Cavity not seen. Negative for T.B.

D. 12 weeks after TPD. "Spot film," cavity very small; bronchus open. Sputum and secretions negative for T.B.

blood-tinged secretions were being sucked from the cavity. Cultures showed *Staphylococcus aureus*. Smears showed that the acid-fast organisms had markedly decreased in numbers. Numerous formed polymorphonuclear pus cells and a few Gram-positive cocci were present. On February 28, four weeks after the start of the transpleural decompression, the secretions were still purulent, about one ounce daily, and contained no acid-fast organisms but many Gram-positive cocci which, on culture, were *Staphylococcus aureus*. At weekly intervals thereafter until May 24, 1940, the smears of cavity secretions continued to be negative for acid-fast organisms. On May 24 the tube was removed.

Repeated cavernograms made March 20, April 26 and May 24 showed that the large cavity had been converted into a fistula (plate 1, B-D). The last cavernogram on May 24 showed that there was no longer any communication with the bronchial tree, although on April 26, 1940 (plate 1-D) a narrowed bronchus could still be demonstrated.

On April 15 cavernoscopy was performed. The walls were smooth and pink and bled on contact with the instrument. The cavity was quite small.

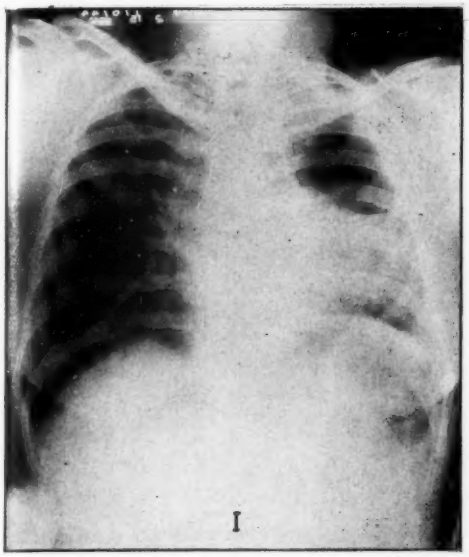
Sputum which was two ounces daily became negative by May 13, on four examinations by direct smear and concentration, and she had no sputum after that date. Her general condition improved during the treatment.

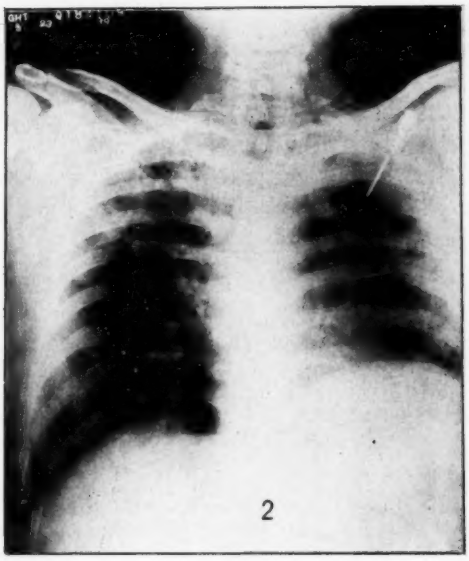
Case 2: C. T. (plates 2, 3 and 4). Bilateral cavities treated with transpleural decompression. Onset of tuberculosis was in 1933, five years before she entered the San Francisco Hospital in January, 1938. She had a severe paroxysmal cough with 4 to 5 ounces of sputum daily. Weight was 130 lbs., but she did not gain. Fever rose to 99.5°F. X-ray films showed a giant cavity on the left with infiltration below it and another area of infiltration in the right upper lobe.

Intracavitary pressures on December 10, 1938 were $-1, +1$, to $-1, +6$. Secretions aspirated from the cavity contained numerous acid-fast organisms and very few formed pus cells. Cultures of the aspirated material showed no growth of aërobes or anaërobes. Methylene-blue introduced into the cavity was readily spat up. Measurement of the intracavitary pressures and injection of methylene-blue were repeated three weeks later with the same results. But when pressure tests recorded on the kymograph were made, artificially elevated intracavitary pressures were maintained, and even after mild decreased pressures no air could then be made to enter the cavity.

Bronchoscopy was performed December 28, 1938 and this showed definite evidence of bronchial tuberculosis with a marked narrowing of the left upper lobe opening and swelling and redness of the mucosa.

On May 23, 1939, a number-14 needle was inserted into the cavity through the first interspace in the mid-clavicular line, and left in place (plate 2, figure 2).





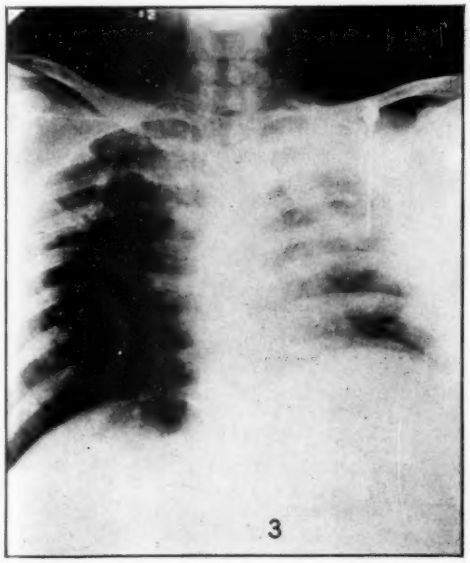


PLATE 2

EXTERNAL TRANSPLEURAL DECOMPRESSION

Case II, C. T. Figure 1, 5–15–39. Large "tension" cavity left upper lobe. Initial intracavitary pressure—0 + 4 cms. water.

Figure 2, 5–23–39. Twelve hours after decompression.

Figure 3, 6–12–39. Three weeks after decompression.

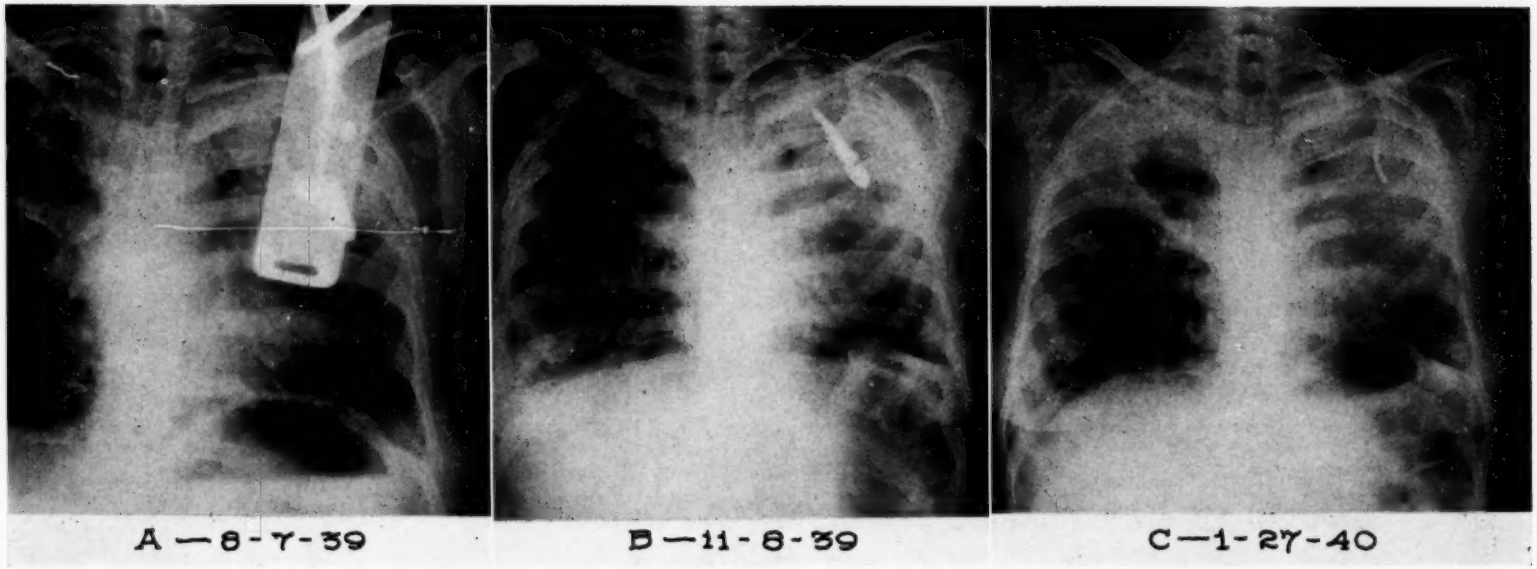
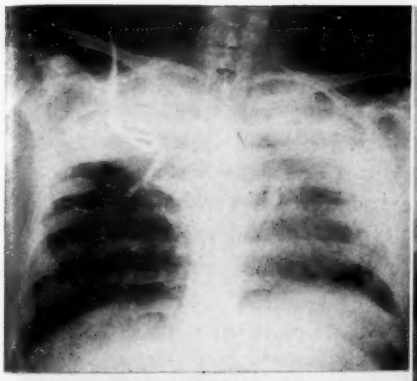
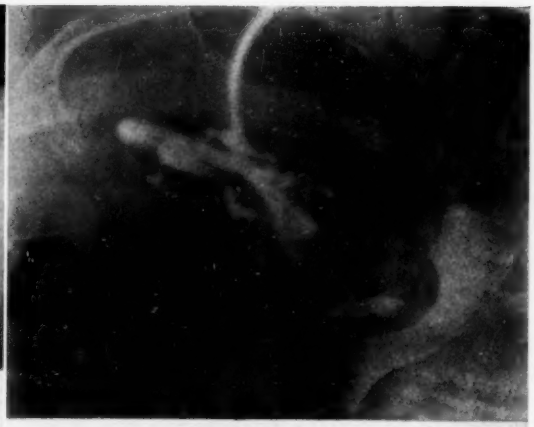


PLATE 3

TRANSPLEURAL DECOMPRESSION (TPD) BILATERAL

C. T., W. female, age 42. Left side.
A. 2½ months after TPD. Secretions negative for T.B. Cavernography shows no broncho-cavernous communication.
B. 5½ months after TPD. Cavernography; no broncho-cavernous communication. Cavity smaller.
C. 8 months after TPD. Secretions negative for T.B. No visible cavity.





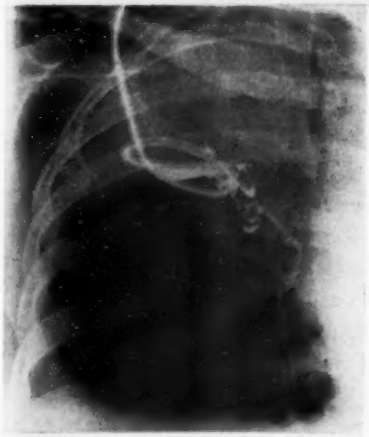


PLATE 4

TRANSPLEURAL DECOMPRESSION (TPD) BILATERAL

C. T., W. female, age 42. Right side.

D. 7 weeks after insertion of catheter into cavity R.U.L. Initial pressure—1 + 3. Secretions negative for T.B. for 3 weeks. Cavernogram shows cavity smaller; bronchus open.

E. 2½ months after TPD. Cavernography showing patent bronchus. Secretions negative for T.B.

F. 3 months after TPD. Cavernography showing patent bronchus. Secretions negative for T.B. Sputum negative for T.B.

Smears of intracavitary secretions again contained only tubercle bacilli and very few formed pus cells. The needle was left open to the atmosphere. On June 23, 1939 the needle was removed, and a metal cannula of larger bore was inserted. The cough and sputum diminished immediately and the cavity decreased in size.

On June 15, kymographic tracings of intracavitary pressures were repeated to test the patency of bronchial communications, and these indicated that a one-way bronchus-to-cavity valve existed, which opened when the pressures in the cavity were artificially reduced to approximately −9, −2 (figure 7).

On July 18, cultures of the intracavitary secretions showed *Staphylococcus albus*. A few tubercle bacilli were still present. By August 7 no acid-fast organisms could be demonstrated in the secretions, which were now frankly purulent (plate 3-A). Subsequent examinations of the smears from intracavitary secretions for six months were all negative for tubercle bacilli but contained numerous Gram-positive cocci.

Cavernoscopic examinations were made in August (plate 3-B) and September and these showed marked diminution in size of the cavity as well as smooth, pink, firm walls which bled easily from the trauma of the instrument. Cavernograms were made in August, November and January (plate 3, A-B) and these showed a progressively diminishing size of the cavity without any bronchial communication. The cavernograms, as well as the X-ray films showed that the large cavity had been converted into a fistulous track.

In November, the metal cannula was replaced by a rubber catheter, which was finally removed on January 27, 1940. The sputum, which was markedly decreased, began to increase again in November and always remained positive. At this time the cavity in the right upper lobe became more prominent and X-ray films on January 27, 1940 showed it to be surrounded by atelectatic lung. On this day a rubber catheter was inserted into the cavity in the right upper lobe and intermittent Wangensteen suction was applied. The pressures were −1, +3. The intracavitary secretions aspirated at this time showed large numbers of tubercle bacilli with very few formed pus cells. Three days later, culture of the secretions from the right side showed staphylococci, and in smears there were numerous Gram-positive cocci. The secretions were frankly purulent. By February 29, the smears were negative for acid-fast organisms. Subsequent examinations at weekly intervals until May 24 were negative for acid-fast organisms.

Cavernograms were made on March 20, April 17, April 29 (plate 4, D-E-F) and May 24. These showed that the cavity had been reduced to a fistulous tract, but there was still a small patent bronchial communication. Under the fluoroscope this bronchus was observed to collapse like an accordion, with expiration (figure 2, ✱2). The sputum diminished markedly following the transpleural decompression of the cavity on the right; it was decreased from 6

5

to 8 ounces to 2 or 3 cc. per day. It became negative on May 13 and on three examinations thereafter.

Cavernoscopic examinations made of this cavity showed the walls to be smooth and pink, containing a few shreds of fibrinous membrane. In June, kymographic tracings of the intracavitary pressures showed that the cavity still retained a one-way valve mechanism from bronchus to cavity (figure 7).

The general condition of this patient has not been satisfactory. She has lost 20 pounds from May, 1939 to May, 1940. Although her sputum is negative and her cavities have been reduced to fistulous tracts, her vital capacity has diminished from 1200 to 600, and she is dyspnoeic with slight exertion. *Cor pulmonale* is suspected.[4]

Case 3: S. T. (plates 5 and 6), aged forty-five. Bilateral transpleural decompression. Onset of tuberculosis in 1930. The patient first entered the San Francisco Hospital in 1935 with a small cavity in the left upper lobe and infiltrations in the left and right upper lobes. A thoracoplasty with removal of the upper four ribs was done at that entry, and he was discharged with a negative sputum in 1936.

He returned to the San Francisco Hospital three years later with an exacerbation of his symptoms, a giant cavity in the right upper lobe and a smaller cavity under the thoracoplasty in the left upper lobe (plate 5-A). He had one and one-half cups of positive sputum, fever as high as 100°F. and a very severe cough.

Bronchoscopy, performed October 9, showed no gross bronchial tuberculosis or stenosis. On October 16 a large metal cannula was inserted into the cavity in the right upper lobe. The initial pressures were -3, $+4$. Secretions aspirated from the cavity showed large numbers of tubercle bacilli and a few formed pus cells. Within a few days, the secretions were purulent and cultures showed haemolytic *Staphylococcus albus*.

Kymographic tracings of intracavitary pressures were performed immediately after inserting the cannula and these showed a highly efficient one-way bronchus-to-cavity valve (figure 8). No suction was applied to the cavity for several months, until January, 1940. At this time Wangensteen suction was started and the metal cannula was replaced by a rubber tube. Later, electric motor suction was used (figure 10).

Four cavernoscopic examinations were made between October and January. They showed a change of the cavity walls from shaggy walls contain-

[4] This patient died very suddenly while drinking a cup of coffee on June 1, apparently with acute myocardial failure. Postmortem examination showed that there were definite findings compatible with *cor pulmonale*. In addition, the cavity on the left had reopened and reached a diameter of 10 cm.; the one on the right had been reduced to a fistulous tract, and its bronchus-cavity relation contained an accordion-like valvular mechanism.

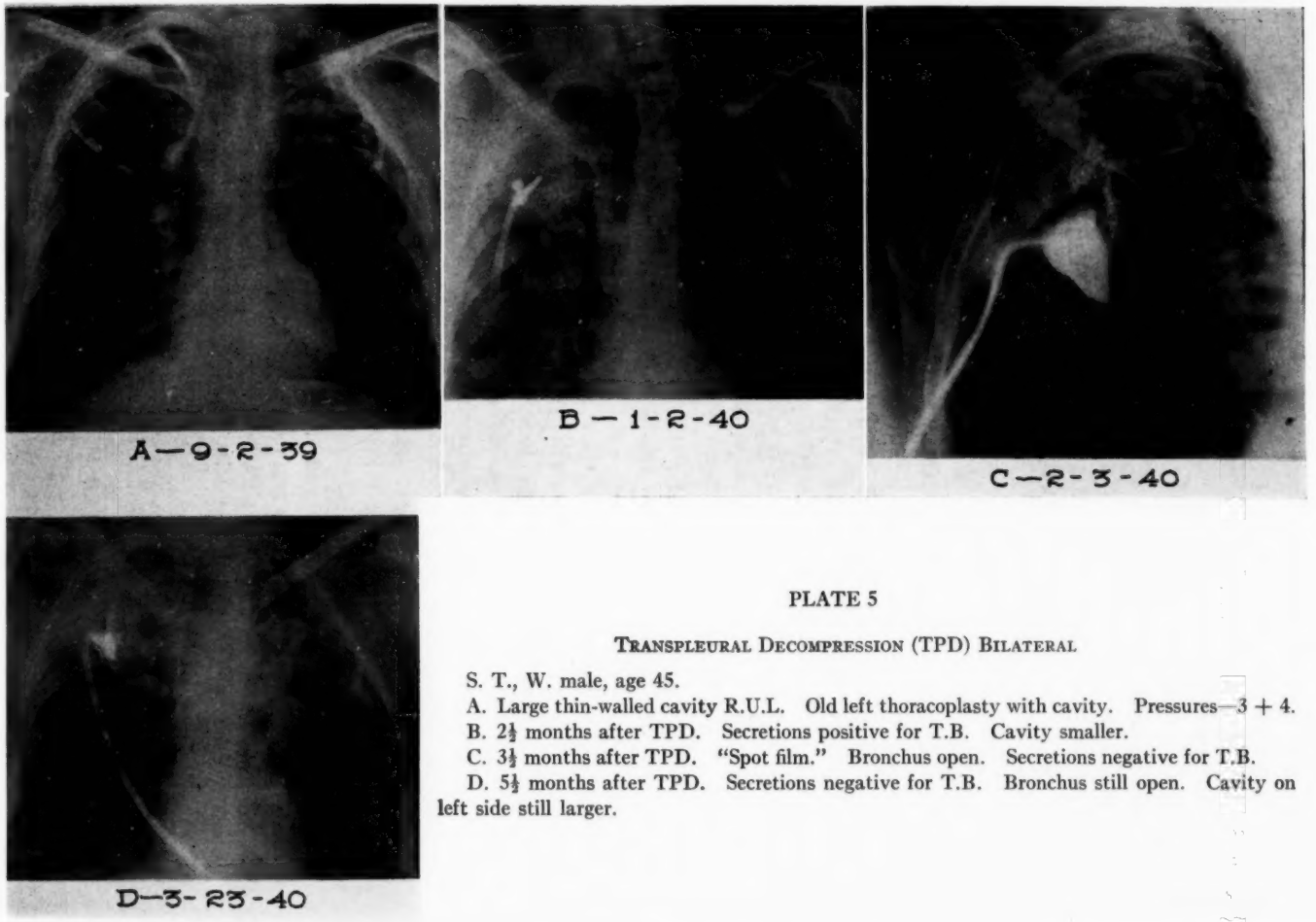


PLATE 5

TRANSPLEURAL DECOMPRESSION (TPD) BILATERAL

S. T., W. male, age 45.

A. Large thin-walled cavity R.U.L. Old left thoracoplasty with cavity. Pressures—3 + 4.

B. 2½ months after TPD. Secretions positive for T.B. Cavity smaller.

C. 3½ months after TPD. "Spot film." Bronchus open. Secretions negative for T.B.

D. 5½ months after TPD. Secretions negative for T.B. Bronchus still open. Cavity on left side still larger.

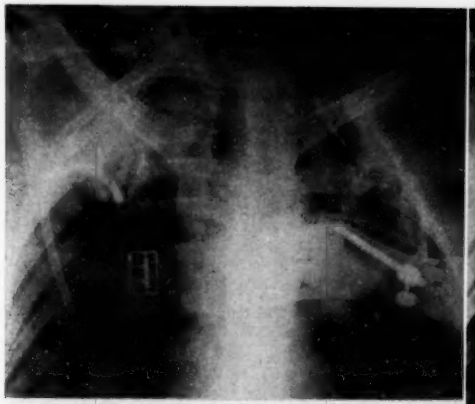


PLATE 6

TRANSPLEURAL DECOMPRESSION (TPD) BILATERAL

S. T., W. male, age 45. Left side.

E. Initial pressure left—4 + 3. Secretions negative for T.B. on the right, strongly positive for T.B. on the left.

F. Cannula replaced by catheter on the left. Cavity smaller. Both sides negative for T.B.

G. Simultaneous serial cavernography. "Spot film" showing bronchus open on right, obstructed on left.

H. "Spot film," left, showing narrow bronchus.

I. Lipiodol on right now in R.L.L., open bronchus. (Sputum and secretions from cavities negative for T.B.) Left bronchus still appears obstructed.

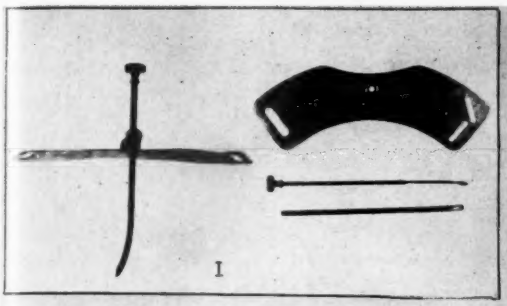
ing fibrinous, adherent exudate to a smooth, pink wall, firm and bleeding with trauma of the instrument. The smears of the intracavitary secretions did not become negative until the latter part of January, 1940. Cavernograms were made in several instances (plate 5, C-D), which showed that the cavity had been converted into a fistulous tract by May 24. There was still present a bronchial communication. The cavity under the left thoracoplasty enlarged somewhat, and on March 30 a metal cannula was inserted in this cavity (plate 6-E). The pressures were -4 $+3$. The smears of the intracavitary secretions showed numerous tubercle bacilli with very few formed pus cells. The secretions became frankly purulent within a few days, and contained *Staphylococci aureus*. Since April 29, the smears from both cavities have been negative for tubercle bacilli.

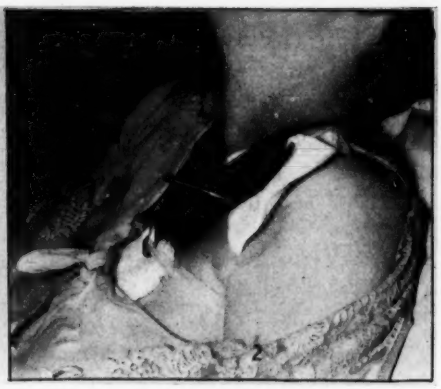
Cavernograms of this left-sided cavity were made on three different occasions and a bronchial communication could never be demonstrated (plate 6,G-H-I). Kymographic tracings of the intracavitary pressures were made on the day the cannula was inserted (figure 10). These indicated that a highly efficient bronchus-to-cavity valve mechanism existed. Cavernograms showed that the cavity had been reduced to a fistulous tract without bronchial communication. On May 24, the catheter was removed.

The general condition of this patient has remained very good. He has gained weight, and his sputum has been converted to negative, being only a few cc. daily.

Case 4: L. F. (plates 7, 8 and 9), aged twenty-nine, had the onset of her tuberculosis in March, 1939 with cough, sputum and loss of weight, all of which were rather mild, but the cough was paroxysmal and severe at times. X-ray films on March 30, 1939 showed a giant cavity in the left upper lobe with infiltration throughout the left lung (plate 7, figure 3). On May 25, a 16-gauge needle was introduced into the cavity; initial pressures were $-1,+2$ and they did not deviate much from this. There was no evidence of an efficient valvular mechanism. The cavity contained practically no secretions and only a few tubercle bacilli were seen on the smears; cultures showed no aërobic or anaërobic contamination. For two weeks there were no changes in the size of the cavity, but cough was markedly diminished and sputum decreased from 30 cc. to 4 or 5 cc. daily (plate 8, figure 4). On June 15 the needle was replaced by a metal cannula with a larger bore (plate 8, figure 5). Secretions became purulent and *Staphylococcus aureus* appeared. Tubercle bacilli were not demonstrated again, even after many examinations, for the next eleven months. The cavity became definitely smaller after the introduction of the trocar, but never completely disappeared. The secretions remained rather scanty for the next three months.

Cavernoscopy showed smooth, pink walls with a small amount of secre-





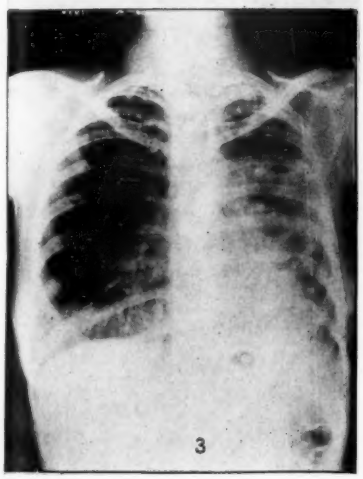


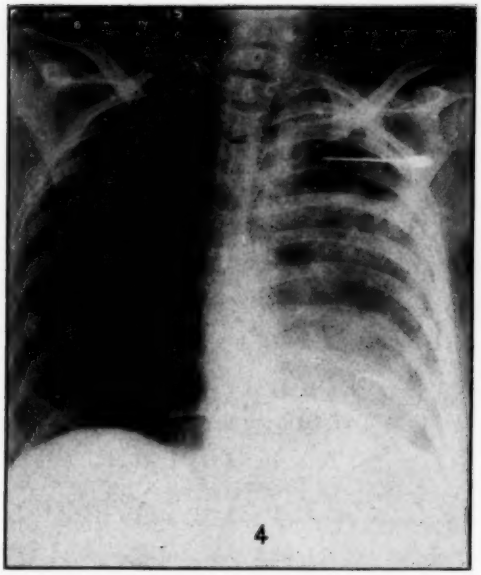
PLATE 7

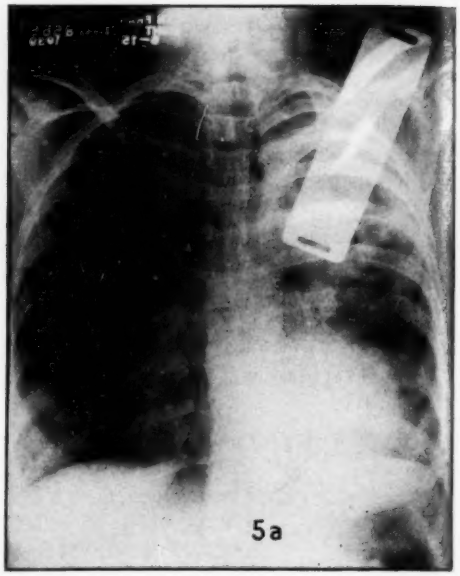
EXTERNAL TRANSPLEURAL DECOMPRESSION

Case IV, L. F. Figure 1. Trocar and shield for cavity decompression.

Figure 2. Patient with trocar in place.

Figure 3, 3-30-39. Large cavity in left upper lobe. Initial pressures—1 + 2.





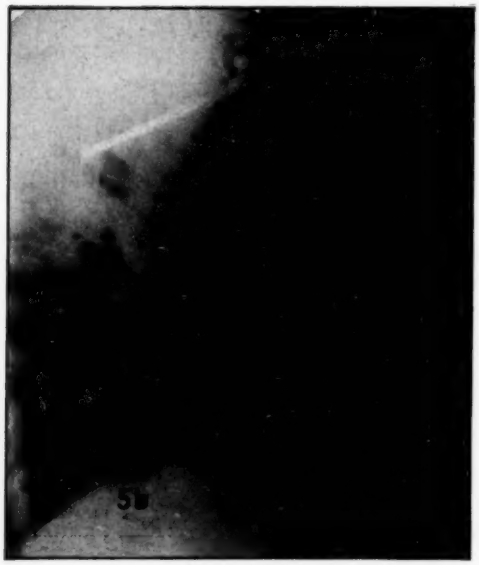


PLATE 8

EXTERNAL TRANSPLEURAL DECOMPRESSION

Case IV, L. F. (continued). Figure 4, 6-5-39. No change in size after decompression.

Figures 5a and 5b, 6-15-39. PA and left lateral. Very little change in size. Needle replaced by trocar.

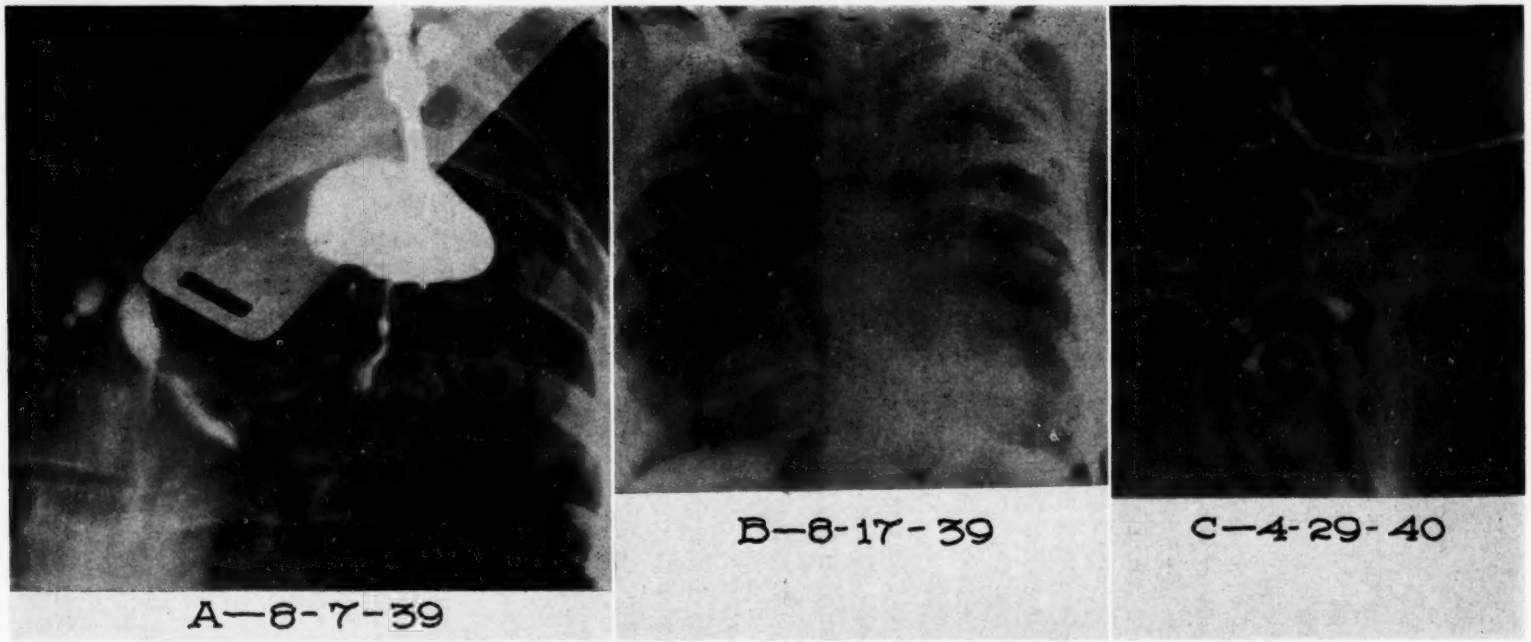


PLATE 9

TRANSPLEURAL DECOMPRESSION (TPD)

L. F., W. female, age 30.

A. 3 months after TPD. Cavernogram shows cavity smaller, is still large.

B. Cavity does not enlarge after ceasing TPD.

C. 11 months after TPD, and 8 months after removal of catheter. Broncho-cavernous and broncho-cutaneous communications still present. Drainage from cavity negative for T.B.

tions. Two areas were seen which were suggestive of bronchus-cavity communications.

On June 16, kymographic recordings of intracavitary pressures failed to demonstrate any valvular mechanism (figure 9). Neither artificially induced positive or negative pressures were maintained.

Cavernograms were made on August 7, 1939 and April 29, 1940 (plate 9, A-C). These showed patent bronchial communications; at least two different bronchi communicating with the cavity were demonstrated. Compared with the X-ray films made on August 17, the cavernograms gave a much more accurate idea of the size of the cavity than the plain X-ray films.

On August 15, the trocar was removed, and a sinus persisted in the skin, intermittently closing during the next nine months. Smears from the draining sinus were negative for tubercle bacilli but contained some staphylococci. The sputum remained positive throughout the course of the treatment until March, 1940. Since this time, it has been negative on several examinations. It remains about 5 cc.

The general condition of this patient has improved. During the course of treatment she gained weight from 104 to 130 pounds. Clinical improvement still continues. In spite of the open cavity and open bronchus, the sputum is negative on direct smears.

RESULTS OF TRANSPLEURAL DECOMPRESSION

Four cavities are apparently permanently converted into fistulous tracts. One of these was treated by transpleural decompression followed by skin flap, the others by transpleural decompresion alone with or without suction. Three additional cavities show secretions negative for tubercle bacilli, but the catheters are still in place. In one additional case, the cavity is still open according to X-ray findings, but the catheter has been removed and the sputum and secretions have been negative for tubercule bacilli for more than six months (L. F., *case 4*). Thus 8 cavities have been sterilized of tubercle bacilli.

Two patients had thoracoplasties after transpleural decompression was discontinued. In both of these cases, the cavities are still open. Four cases had thoracoplasties prior to transpleural decompression. One of these patients is apparently cured (4). In one, transpleural decompression has been discontinued, the cavity is very small and reduced to a blind fistula, and the secretions have been negative for tubercle bacilli for more than a month (S. T., *case 3*). In the third and fourth cases, the cavities are smaller, but the secretions are still positive for tubercle bacilli.

The cases that we chose for transpleural decompression were far advanced bilateral cases for the most part, with or without tension, or "blocked," cavities, and all deemed unsuitable for the usual compression therapy. This was particularly true of the 2 bilateral cases (S. T. and C. T.). All 4 cavities in these 2 cases are either converted to fistulous tracts or small cavities and no longer discharge tubercle bacilli.

COMMENT

The mechanism of healing of cavities treated by transpleural decompression may be described in three parts, each of which is separate from the other two. The first of these is the stabilization of the intracavitary pressures at or below atmospheric pressure; this is purely physical. The second is the disappearance of tubercle bacilli from the discharge; this is biological. The third is the conversion of the ulcerative tuberculous cavitary process into a fistulous tract; this is a pathological process (10).

Stabilization of Intracavitary Pressures: Adequate foundation has already been given in this paper for our changing concept of the maintenance of cavities. Formerly we believed that cavities were largely maintained by a balance of destruction instituted by the tuberculous infection, on the one hand, and healing processes dependent upon the resistance of the individual, on the other. Some evidence for this view occurred in the elastic tissue found in the sputum, which indicated more or less continuous destruction of lung. Now, however, from our observations and knowledge of the indolence of the tuberculous infection in cavities, we believe that other factors are more important in the maintenance of the tuberculous cavity. Most important of these, we believe to be the one-way bronchus-to-cavity valve mechanism, with its resulting entrapping of air. The efficiency of these valves determines, we believe, to a great extent the results of compression therapy. Nonvalvular cavities, which are maintained by factors other than bronchus-to-cavity valve mechanisms, usually respond well to collapse or compression therapy (figure 2, #5). Tension, or "blocked," cavities with very efficient bronchus-to-cavity valve mechanisms respond poorly to collapse therapy but respond well to transpleural decompression therapy.

The rôle of both decompression therapy and compression therapy in bringing about the disappearance of cavities is to alter the effects of the respiratory trauma within the cavities, that is, to alter the fluctuating pressures so they become stable. In transpleural decompression, whether or not we applied suction to the catheter or cannula introduced into the

cavity, the cavities became smaller. Both suction and introduction of the constant unchanging atmospheric pressure prevent the large fluctuations of pressure that occur during slight movements of the patient such as talking or swallowing and, particularly, those sudden, large changes in pressure associated with cough. We observed that the transpleural decompression nullified the deleterious effects of cough and movements so that the cavities were placed at true physiological rest. We believe, to a great extent, that the usual compression therapy, such as thoracoplasty, artificial pneumothorax and phrenicectomy all bring about their beneficial effect chiefly because they tend to neutralize the harmful effects of respiratory trauma (2), and to substitute stabilized pressures within the cavities. Poor results of compression or collapse therapy may occur if bronchus-to-cavity valve mechanisms are so efficient that they continue to allow high pressures and fluctuations of pressures to exist within the cavities in spite of the therapy.

Disappearance of Tubercle Bacilli from the Cavities: From a purely bacteriological standpoint, we have been able to confirm Coryllos' findings (3, 10) that the tubercle bacillus alone inhabits the tuberculous cavity in the living patient, at least in 18 upper lobe cavities which we examined. During the course of transpleural decompression, many cavities still remained open cavities with open bronchi, but did not continue to discharge tubercle bacilli into their secretions. In fact, in our 8 cavities sterilized with transpleural decompression, the cavities were always present though diminished in size at the time when tubercle bacilli could no longer be demonstrated in the secretions.

Coryllos and Ornstein (10) implied that oxygen transmitted to cavities by open bronchi enhances the multiplication of tubercle bacilli, and this fact is given as evidence for believing that bronchial obstruction with a resultant anoxia of cavities is necessary for their disappearance. We observed that tubercle bacilli disappeared from the cavities under transpleural decompression when oxygen with atmospheric tension freely communicated with the cavity. In these cavities no low oxygen tension could have resulted, and yet the tubercle bacilli disappeared.

It seems to us, therefore, that some other factors must be held accountable for the disappearance of the tubercle bacilli. At the present time we believe that tuberculous cavitary infection does not produce large numbers of pus cells in the intracavitary material. Some evidence for this is seen in examining the smears of secretions obtained from the

cavities undergoing transpleural decompression. At first the secretions contain large numbers of tubercle bacilli with detritus but without numerous formed pus cells. Within a few days the secretions are purulent, containing numerous pus cells, mostly polymorphonuclear cells and fewer tubercle bacilli. Usually within six weeks the secretions are frankly purulent, containing *Staphylococcus aureus* without tubercle bacilli. As time goes on and the cavities decrease in size, the amount of purulent drainage decreases and sometimes becomes serous. It thus appears to us that the granulomatous nature of the original tuberculous infection of the cavity is altered as a result of the transpleural decompression and the secondary staphylococcus infection.

Observations of the amount of material aspirated from the cavities were made. The amounts varied from day to day and from cavity to cavity. There was no accurate correlation of the amount of drainage with the size of the cavity or the amount of sputum previously raised, early in the course of the transpleural decompression. But as time went on, for example, after one or two months, size of cavities, drainage and sputum usually all diminished; usually the size of the cavity diminished first, then the sputum and last the cavity drainage.

We feel that both the altered intracavitary inflammatory reaction and the mechanical removal of the intracavitary secretions are in some way associated with the disappearance of the tubercle bacilli.

Conversion of the Cavity into a Fistula: By means of many serial cavernograms, we have shown that the cavities treated by transpleural decompression undergo a morphological change. In our cavities, treated by transpleural decompression, the cavernograms show a progressive alteration from more or less round or oval larger cavities to smaller cavities or fistulous tracts. Pagel (11) has shown that these fistulous tracts may be the end-result of healed cavities not treated by transpleural decompression. That these fistulous tracts are frequently not held firmly united by scar tissue, was also shown by Pagel (11). We observed in 8 cavities that the tubercle bacilli disappeared from the draining secretions when the cavities were smaller, but before they were converted into fistulous tracts. In 5 sterile cavities we have not observed diminution in size to that of a fistula. In 2 cavities whose secretions are negative for tubercle bacilli the cavities were reduced to the size of fistulae. The permanence of the result of our cavities treated by transpleural decompression is questionable since we do not know the histological changes in

the walls of the fistulae or small cavity. We can expect that many cavities now thought to be permanently converted into fistulous tracts will reappear. Thoracoplasty after transpleural decompression may, therefore, be an aid to permanent conversion of the cavity into a fistulous tract.[5]

SUMMARY AND CONCLUSIONS

Observations of cavities are presented which form the basis for our concept of their behavior. According to this concept, the maintenance of most cavities is dependent upon the presence of bronchus-cavity valves which allow the passage of air predominantly or even totally in one direction, that is, into the cavity. These valves produce abnormal tensions within the cavities. Cavities tend to disappear when this abnormal tension is stabilized at or below atmospheric tension. Compression (collapse) therapy may augment the tension in these cavities when the bronchus-to-cavity valves are highly efficient. Transpleural decompression therapy tends to stabilize the pressures in these cavities at atmospheric or negative pressures. Compression (collapse) therapy, in the absence of highly efficient bronchus-cavity valves, also tends to stabilize the intracavitary pressures. True physiological rest is induced when stabilization of the intracavitary pressures is produced.

The tuberculous infection in cavities is not usually pus producing. In cavities treated by transpleural decompression, tubercle bacilli disappeared from the draining secretions in 8 out of 20 cavities. The mechanism of the disappearance of the tubercle bacilli is discussed.

The morphological changes of cavities undergoing transpleural decompression is demonstrated by cavernograms. The nature of the disappearance of these cavities is discussed.

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[5] Since the paper was written, thoracoplasties have been performed upon 4 patients, 2 of whom are reported here in detail, Case L. F. and Case E. E. The reasons for thoracoplasty were the enlargement of the fistulous tracts into the cavities following the removal of the tubes (two cases), or the failure of the cavities to diminish greatly in size, although the secretions contained no tubercle bacilli (two cases). In all 4 cases the early results of thoracoplasty are good.

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RESULTS OF COLLAPSE THERAPY[1, 2]

A Follow-up Study of Two Groups of Patients Treated between 1926 and 1938, respectively, with and without Collapse Therapy. Data about Life Expectancy and Hospital Mortality Rates

B. P. POTTER

For at least a decade before Drolet's report (1) on "Present Trend of Case Fatality Rates in Tuberculosis," the lay and professional public was encouraged to believe that the modern treatment of pulmonary tuberculosis had played a significant part in prolonging life, if not actually reducing the number of deaths by permanent control of the disease. I was one of many who were most amazed to learn that this impression was apparently unfounded when I heard Drolet's paper for the first time in November, 1937, before the Eastern Section of the American Sanatorium Association. In fact, I remember vividly the lively discussion that followed, and how in spite of the convincing figures given, the conclusions were questioned by one discussant after another. Since then several papers (2, 3, 4) have appeared and the subject has had wide unpublished discussion.

The question under consideration is now as it was originally so well expressed by Drolet in the following statement: "With declining cases and deaths a common observation, there can be little question but that, between improved conditions of life and increasing provisions for the sick, some control of the infection is obviously being achieved. On the other hand, is definite progress being made in the treatment of the disease now that there is available in many places a number of hospital beds sufficient to receive most of the active cases who seek public care, and that of late, new and radical forms of surgical treatment are being used in an increasingly greater proportion of the patients? What effect if any, have these facilities and measures had upon the case fatality rates in tuberculosis?"

To determine this effect, Drolet chose the ratio of total deaths to reported new cases as his yardstick, a measure which, as will be shown

[1] Presented at a joint session of the National Tuberculosis Association, American Trudeau Society and the American Association for Thoracic Surgery, Cleveland, Ohio, June 6, 1940.

[2] From the Hudson County Tuberculosis Hospital, Jersey City, New Jersey.

further on, could not lead to deductions other than he reached. Furthermore, we cannot accept the method of study suggested by his statement "the existence already of quite a number of adequate investigations suggest that there is *perhaps* (italics are mine), a greater finality and completeness in the community's record, rather than in those of the hospitals alone, for appraising the influence of the sanatorium and surgical treatment of tuberculosis"—for the simple reason that we seriously question the presupposed existence of uniformity of such factors as reporting, adequacy of treatment, extent of collapse therapy and local conditions.

Our study, as listed below, concerns 3,077 patients divided into two groups; one consisting of 1,458 cases treated during the period from 1926 to 1932 when 6.2 per cent received collapse therapy, the other numbering 1,619 patients treated in the interval between 1932 and 1938 when 61.2 per cent of the admissions were subjected to one or a combination of the procedures of pneumothorax, phrenic interruption and thoracoplasty.

*Classification of 3,077 patients treated between 1926 and 1938 according to therapeutic indications**

Groups	1926–1932	1932–1938
Infiltrative lesions and small cavities	139	151
Collapse group:		
Received therapy	90	992
Should have received therapy	777	0
Extensive disease such as to prohibit any active therapy	452	476
Total	1,458	1,619

* Criteria for therapy: The infiltrative form of pulmonary tuberculosis with negative sputum is treated by the usual rest regimen, unless cavitation or progression takes place during treatment. When, however, a patient presents infiltration, a positive sputum and disputed evidence of cavitation, he is placed in the "small cavity group" (2 cm. or less) in which, with few exceptions, collapse therapy is favored only after a liberal period of bed-rest. Where the cavity is larger, collapse in one of its forms is immediately resorted to, unless there are contraindications.

To avoid criticism raised in other instances, we wish to stress the following points:

First, that in classifying the stage of the disease we reviewed the roentgenograms of the cases herein reported and used the present criteria as outlined by the National Tuberculosis Association. The course of the disease in each case was followed either by study of serial films and/or by clinical observations.

Second, the cases in both groups are comparable with respect to age and extent of tuberculosis. Thus the average age was 24.5 years, and

the vast majority of the patients was between eighteen and forty years. Far advanced disease was encountered in 88 per cent in each group.

Third, in the important period between 1932 and 1938 only 19 patients could not be traced.

Since it is our purpose to evaluate the effect of collapse therapy by comparing the fate of the patients in the two groups shown above, we propose to analyze first the 1,619 cases treated in the six years between 1932 and 1938. In these tuberculosis became controlled by bed-rest alone in 151 patients, in 476 others the prognosis was hopeless on admission and the remaining 992 were candidates for collapse therapy. The discussion which follows deals therefore with the latter patients, as summarized in table 1.

TABLE 1

Fate of 992 patients subjected to collapse therapy from 1932 to 1938

STATUS	WORKING OR AMBULANT	IMPROVED	UNIMPROVED OR WORSE	LOST	DEAD
Effective collapse 378 (38.1 per cent)	323	32	7	3	13
Pneumothorax unavailable or abandoned and other forms of collapse ineffective 553	81*	59	157	16	240
One side effective cavity present in contralateral lung 61	30	14	13	0	4

* Cavity closed spontaneously in 49 patients.

By contrast one should carefully examine the figures for the abandoned and ineffective group. Of the living patients that we have been able to follow, all but 49 in whom the cavity closed spontaneously, have open lesions. The most important feature, however, is the comparative number of deaths in the two groups.

It may be argued that the favorable results in the patients with effective collapse are only immediate ones. For this reason we include a study of 432 patients in the Out-Patient Collapse-Therapy Clinic who have been followed since their discharge from the hospital. These have been observed from one to seven years; the majority longer than four years. In this number are also included 100 reëxpanded cases. Obvi-

ously, as listed below, the relative number working and ambulant closely parallels that of the patients listed above. As a matter of fact, if those working were to be separated from the ambulant group, the later results would show a higher percentage able to work, because many of those discharged ambulant or improved eventually recover enough to return to work.

Follow-up of 432 patients in the out-patient collapse-therapy clinic

Working and ambulant	385
Improved	18
Unimproved or worse	5
Dead	24

In the light of these findings, we are now prepared to analyze the 1,458 patients treated in the interval between 1926 and 1932. As already mentioned, the stage of tuberculosis and the indications for collapse therapy were reclassified according to present standards, so as to conform with the cases managed between 1932 and 1938. As is evident from the listing that follows, 109 patients must be left out of consideration because we could not trace them. Of the remaining 1,349 cases, we found 801 in whom collapse therapy should have been attempted and in whom according to table 1, an effective collapse could have been anticipated in 38.1 per cent or 305 patients.

Status of 1,458 patients in 1932 treated since 1926

Living	323
Dead	1,026
Lost	109
Total	1,458

But, what is most significant, and again by reference to table 1, only 3.4 per cent of the 305 patients, or 10, should have been dead at the end of the six-year period in question instead of 222 patients, as is actually the case. Another valuable point in this respect is offered by a comparison of the total deaths in the group of cases in the period between 1932 and 1938 and that during 1926 and 1932 which indicates a death rate of almost twice as many in the latter interval (table 2). We do not mean to imply by this statement that the results in effective collapse therapy are entirely responsible for the difference in the total death rates in the two periods, for more energetic application of bed-rest and the clinical improvement in the ineffectively collapsed cases which not infrequently followed, served to prolong life in the patients treated in the later years.

Finally, there is to be considered the effect on the case fatality rates by the difference in management of the disease in the two periods under discussion. At this juncture we wish to reiterate that Drolet's conclusions based on the ratio of deaths per reported new cases could not have been otherwise because he calculated *all* deaths in any one year and not the deaths that occurred among the new admissions. We insist that in doing so he included deaths of patients left over from previous years, practically all of whom, as we have shown above, formed the group in

TABLE 2

Total deaths in the two groups of cases under discussion

GROUP	CASES	DEATHS	PER CENT
1926–1932	1,349*	1,026	76
1932–1938	1,600*	708	44.2

* Difference between 1,458 and 1,349, and 1,619 and 1,600, respectively, comprises the cases that could not be traced in each group respectively.

TABLE 3

Total annual deaths in hospital

YEAR	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937
Total deaths	82	102	78	73	71	88	83	60	70	67	61	70

TABLE 4

YEAR	1926	1927	1928	1929	1930	1931	1932	1933	1934	1935	1936	1937
Number of new admissions	248	228	227	214	265	253	259	254	231	278	265	231
Number of deaths	50	69	68	57	48	49	48	38	37	39	38	25
Percentage of deaths	20	30	30	26	18	19	18	15	16	14	14	10

which the prognosis was hopeless to start with or in whom collapse therapy had failed. Thus, (table 3) while the total annual deaths are lower in the corresponding period, the constancy of the trend is not as impressive as that among the new admissions (table 4). To ascertain the probable effect of modern treatment of tuberculosis on prolongation of life one should consider the yearly deaths among the new admissions separate from the total deaths. By following this contention we find (table 4) that the annual death rate among the new cases is strikingly lower for the period between 1932 and 1938.

CONCLUSIONS

We believe that we have presented sufficient evidence to show that the total deaths over a period of years and the yearly deaths of new cases in patients with and without collapse therapy is decidedly lower in the former group. We feel further that if the modern treatment of tuberculosis were practiced to the same extent and character throughout the country as it is in the scattered accepted clinics, this trend would exhibit itself more universally.

At the same time it must be admitted that the results of collapse therapy are not reflected upon the community reports because they are overshadowed by the deaths of the great number of hopeless or nearly hopeless far advanced cases admitted to tuberculosis institutions. This fact, however, does not warrant the conclusion that institutional treatment, supplemented by collapse therapy, has not served to prolong life.

Lastly, we would stress that it is not to be taken that collapse therapy was the only factor responsible for the lower mortality rates. We concede that other conditions played an important rôle, yet we insist that the significant influence of modern treatment is not to be denied.

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INSATIABLE PNEUMOTHORAX[1]

EPHRAIM KOROL[2]

REVIEW OF THE LITERATURE

In 1930 Burnand (1) reported that in some 5 per cent of cases coming to him for artificial pneumothorax treatment, he was unable to produce a pneumothorax visible on the roentgenogram in spite of large and repeated injections of air into the pleural cavity. The water manometer was used to locate the pleural space and satisfactory readings were obtained before air was inflated, but no matter how much air was injected, no pneumothorax could be established. Burnand observed that in these cases emphysema was present. He thought the pleural membranes were healthy and were absorbing air more rapidly than usual. He recommended the production of a mild pleurisy by means of instillation of oil of gomenol, in order to retard the absorption of air from the pleura.

Soon after Burnand's paper many other articles (2, 3, 4, 5, 6, 7, 8, 9, 10) began to appear in French, Italian and Spanish, dealing with this subject and referring to the condition as insatiable pneumothorax, guzzling pneumothorax, pleural incontinence, pleural porosity, *etc.* Most of the writers emphasized the association of this condition with pulmonary emphysema, asthma and bronchial spasm, and believed that the patients suffered from increased vagus tone which causes an increased vascularization of the pleura and increased absorption of air. Belladonna was recommended to depress the vagus and it was used successfully by several authors.

Lucacer (2, 3) reports 8 cases in detail. The manometer showed negative pressures, lower in inspiration, before each gas inflation. In two cases a further drop in pressure was observed during the treatment, attributable to ruptured pleural adhesions. Nevertheless, no pneu-

[1] Published with the permission of the Medical Director of The United States Veterans Administration, who is not responsible for the conclusions drawn and the opinions expressed by the author.

[2] Veterans Administration Facility, Batavia, New York.

mothorax pockets were demonstrated. In some cases over twenty inflations were made without achieving a roentgenologically demonstrable pneumothorax. The treated lungs appeared "hyperdiaphanous" due to emphysema, but there was no separation of the lung from the chest wall. Lucacer then gave his patients a course of 6 to 12 daily hypodermic injections of Bellafolin and as a result of this treatment a successful pneumothorax was finally achieved in each of the 8 patients.

Silvestri (4) reported similar results after the administration of Bellodonal, while Anzalone (5) used Bellafolin with success. Pastor and Bence (6) and Basunti and Lenci (7) reported the use of atropine in such cases with benefit.

Boldacci (11) experimented with dogs to investigate the effect of atropine on the rate of absorption from the pleural cavity and determined that in vagotonic dogs the absorption of gas is increased in rate. Atropine delays absorption while physostigmin has the opposite effect.

Warembourg and Swynghedauw (12) made observations on patients with selective pneumothorax and they obtained results which are at variance with those of Boldacci. In 22 of 36 experiments the intrapleural pressure rose after intramuscular injections of atropine and there was a tendency of the normal lung to expand under atropine. Similar results were obtained by Brill, Prinzmetal and Brunn (13). It should be pointed out however that Warembourg *et al.* and Brill *et al.* were dealing with normal and not emphysematous individuals. It may well be that in cases of emphysema with bronchial spasm the administration of atropine may affect the volume of the lungs more than the girth of the chest, and this would alter the intrapleural pressure.

PHYSIOLOGICAL CONSIDERATIONS

The behavior of the pneumothorax gasses has been studied by many observers and is well understood. Immediately upon its entry into the pleural cavity the air begins to diffuse into the tissues in accordance with the physical laws governing the diffusion or gasses through liquids (14). Oxygen is rapidly taken up by the pulmonary capillaries while carbon dioxide passes into the pneumothorax. The nitrogen exchange proceeds more slowly. After a few hours the composition of the pneumothorax gas becomes similar to that of the alveolar air (15).

The rate of absorption varies directly with the size of the chest and the healthy state of the pleura and inversely with the degree of lung collapse. Bodily exercise increases the absorption. In the average adult

with healthy pleura the rate of absorption has been found to vary from 40 cc. (16) to as much as 110 cc. (17) and 127 cc. (18) daily. Inflammatory changes in the pleural membranes and underlying tissues cause a delay in the gaseous exchange. There is no known physiological or pathological state that will permit the instantaneous absorption of large quantities of air from the pleural cavities, as is alleged to occur in the condition under consideration.

OBSERVATIONS

We have records of two patients who were considered cases of insatiable pneumothorax and were given air inflations over a period of months without X-ray signs of pneumothorax.

The manometric signs were usually unsatisfactory, suggesting that the needle was in lung tissue; but frequently a reading of -4, -6 or -3, -5 was obtained which after instillation of 200 cc. of air might change to $+1$, $+3$. At other times the pressure was not altered by as much as 500 cc. of air. Neither patient could learn to hold his breath with glottis open and when the manometer reading was unsatisfactory, we could not be certain as to whether the needle was in a space, closed or open to the atmosphere. The patients demanded continuation of the refills and were gratified with the tight feeling in the chest which they claimed after each treatment. The physical signs were inconclusive as there were hyperresonance and feeble breathing over the lung base, as a result of emphysema, and pneumothorax could not be ruled out. After we became skeptical as to the existence of pneumothorax, certain examinations were made which convinced us that no pneumothorax was ever induced in either case and that all the injections of air were made into emphysematous bullae. One case will be described in some detail.

CASE REPORT

The patient first presented himself for treatment on April 1, 1932, at the age of thirty-six. He was examined at the United States Veterans Facility, Lincoln, Nebraska, and was found to have a moderately advanced fibroid lesion in the upper half of the right lung without cavity formation. He improved under rest treatment. Six years later he entered the Veterans Administration Facility, Leavenworth, Kansas, following a pulmonary haemorrhage. He received pneumothorax treatments and about 12 air injections were given. On April 8, 1938 he reported to the Pneumothorax Clinic of the Veterans Administration Facility, Lincoln, Nebraska, for an air refill which was overdue. The needle was inserted into the sixth interspace

anterolaterally at the site of the previous operations. The manometer registered −4, +2. The location of the needle was uncertain. When the patient was asked to hold his breath with glottis open, the manometer showed +6. It was suspected that the man could not open the glottis while holding his breath, as his abdominal muscles would not relax during the attempt. A syringe was applied to the pneumothorax needle and, as upon suction no blood but air was drawn, it seemed safe to proceed with the inflation of air. After

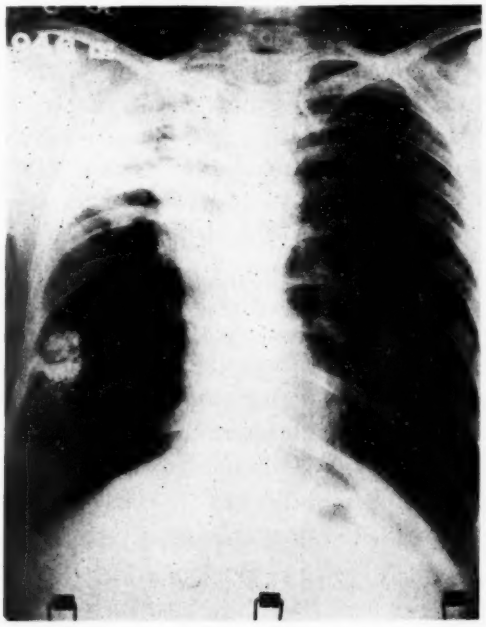

FIG. 1. Lipiodol injected through chest wall into "insatiable pneumothorax." A large bulla is half full of the opaque substance, some of which has escaped into adjoining lobules. A spastic bronchus can be seen just above the 5th rib anteriorly. There is a streak of lipiodol in the tissues parallel to the 7th rib. No lipiodol in pleural cavity.

200 cc. the reading was −2, +4. It was thought that the injection was made into a small pneumothorax pocket. Fluoroscopic examination, however, failed to show the pneumothorax. The roentgenograms made at the Leavenworth Hospital were obtained for examination and they also failed to show any collection of air between the chest wall and the right lung.

During the second treatment the needle was inserted in the right posterior axillary line. The manometer was −4, −2, and 200 cc. of air were given with resultant positive pressure. Fluoroscopic examination showed no pneumothorax. The physical signs were coarse moist râles with bronchial breathing

above the third rib and sixth dorsal vertebra. Over the base of the lung there were hyperresonance and feeble vesicular breathing. The roentgenogram showed several cavities with much fibrosis and contraction of the upper half of the right lung and extensive emphysema at the base.

The next operation showed a reading of −4, −2 and following the injection of 150 cc. of air some subcutaneous emphysema was felt and seen fluoroscopically but no pneumothorax. At the patient's insistent request several more air inflations were made. On May 5, 1938 a reading of −3, 0 was obtained. A syringe containing 5 cc. of warmed lipiodol was attached to the pneumothorax needle and the lipiodol was injected into the air pocket, and the injection was continued as the needle was slowly withdrawn from the chest. Fluoroscopic examination showed most of the lipiodol in a large bulla in the middle lobe of the lung. As the patient coughed, the lipiodol was seen to ascend into a narrow bronchus and to invade neighboring lobules. There was a streak of the opaque substance in the subpleural tissues. No lipiodol had found its way into the pleural space. (See figure 1.)

SUMMARY

In a case of tuberculosis of the right lung of six years' duration the upper and lower lobes had undergone much fibrosis and excavation while the middle lobe became emphysematous. Many pneumothorax treatments were given but no pneumothorax was established. The condition of insatiable pneumothorax was thought to exist, but upon the injection of lipiodol into the "pneumothorax," it was determined that the air inflation had been given into emphysema vesicles and not into the pleural cavity.

PITFALLS IN THE USE OF THE MANOMETER IN PNEUMOTHORAX THERAPY

We believe that the several writers were led to the erroneous diagnosis of insatiable pneumothorax by overconfidence in the manometer as a guide to the pleural cavity.

In the absence of emphysema the intrapleural pressure is less than atmospheric. The normal lung is smaller than the chest and is kept stretched to fill the chest cavity. When an opening is made into the pleural cavity, air rushes in and the lung retracts from the chest wall. When the manometer needle enters the pleural cavity, whether or not the lung is punctured, air is sucked from the manometer into the chest and a negative pressure is recorded, the suction effect being greater in inspiration than in expiration. If no pneumothorax is produced, due to obliterative pleurisy, and the needle lodges in the lung, the intrapulmonic pressure will be registered: a slight negative reading in inspiration, a

slight positive reading in expiration. In cases of localized or generalized enphysema the overdistended lung, upon opening the chest, may fail to collapse; it may even bulge outside of the thorax. In such cases the manometer needle correctly placed in the pleural space will not show the expected rise of the fluid column in the manometer. Moreover, in these cases the intrapulmonic pressure is also abnormal. Bronchial stenosis is often present. With complete bronchial occlusions the pressure in the lung cavity may be found subatmospheric, in partial stenosis the pressure may be considerably above atmospheric (19, 20).

The von Muralt Test: When the manometer readings are unsatisfactory the operator asks the patient to hold his breath with glottis open: if the needle is in the pleural cavity the pressure remains negative; if the needle is in the lung cavity in communication with the atmosphere, the pressure drops to zero. It is easy to see that this test is likely to be misleading in case the needle is in an emphysematous lobule. In this connection it must be emphasized that most patients are not able to relax their glottis and abdomen when holding their breath. The maneuver requires considerable training and intelligence on the part of the subject and generally cannot be accomplished on the operating table. Marek (21) and Hinterreger (22) have emphasized the fallibility of this test.

THE CURE OF INSATIABLE PNEUMOTHORAX BY BELLADONNA

It is well known that the emphysematous lung offers resistance to the creation of a pneumothorax and the lung will remain inflated even after the chest is laid wide open. In the living subject this resistance is due in part to bronchial spasm, and in the presence of asthma and bronchitis, to accumulation of secretions in the bronchi, which factors interfere with the egress of air and collapse of the lung. Granting that the phenomenon of insatiable pneumothorax is due to emphysema, it can be understood why in some cases a good pneumothorax may eventually be established after the liberal use of atropine and other bronchodilators.

SUMMARY AND CONCLUSIONS

1. The known laws governing the diffusion of gasses in the tissues make it impossible to accept the reality of insatiable pneumothorax.

2. In the cases of insatiable pneumothorax described in the literature, the futile air injections were made not into the pleural cavity, but into emphysematous bullae which existed in all cases.

3. In cases of emphysema the manometer is an unreliable guide to the

pleural cavity. In these cases the pressure relations may be reversed, that is, the intrapleural pressure may be above atmospheric and the intrapulmonary pressure may be subatmospheric.

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TUBERCULOUS EMPYEMA[1]

Type of Collapse and Extent of Disease as Factors in Its Onset

I. L. CUTLER

The purpose of this paper is to show the incidence of tuberculous empyema without other organisms, complicating mechanically poor pneumothoraces as compared to that occurring in patients having mechanically effective pneumothoraces in the same stages of disease.

With the wide-spread use of artificial pneumothorax in the treatment of pulmonary tuberculosis we should not lose sight of the fact that pneumothorax may be a double-edged sword; that it may be most beneficial and on the other hand may give rise to complications which are debilitating or dangerous. Tuberculous empyema is foremost among these and it is just as important to know when to discontinue a pneumothorax as to know when to induce it.

I shall endeavor to demonstrate that mechanically poor collapses give rise to a much higher percentage of empyema than mechanically good collapses when considered in similar stages of disease, and that many such empyemata could have been avoided if pneumothorax had been abandoned prior to the onset of effusion.

There are many explanations for pleural effusions; the most widely accepted one to-day is direct infection of the visceral pleura from the underlying pulmonary tuberculosis. I believe that two other factors, namely, the type of collapse and the extent of disease, play important rôles. Coryllos (1) associates tuberculous empyema with tearing of adhesions and bronchopleural fistula. The tear occurs at the weakest point which is at some diseased area in the visceral pleura which is relatively thin in comparison to the parietal pleura.

METHOD OF STUDY

A total of 476 pneumothorax cases at Rutland State Sanatorium from January, 1935 to April, 1940 inclusive were reviewed. These pneumothoraces were of six months' duration or more.

[1] From Rutland State Sanatorium, Rutland, Massachusetts.

Group 1 comprises the mechanically good pneumothoraces in which the collapsed lung was not adherent to the chest wall. Seventeen per cent of this group were of six months' to one year's duration while 83 per cent had been maintained for from one to five years. Pneumonolysis had been performed 203 times in this group.[2]

Group 2 comprises the mechanically poor pneumothoraces in which the diseased lung was adherent either *en masse* or by numerous or very thick adhesions to the chest wall as determined by X-ray or thoracoscopy.

The diagnosis of pure tuberculous empyema was based on finding a turbid or purulent fluid that was positive on direct smear for tubercle bacilli.

TABLE 1

	TOTAL CASES	TOTAL TUBERCULOUS EMPYEMATA	PER CENT	STAGE I			STAGE II			STAGE III		
				Total Cases	Total Tuberculous Empyemata	Per cent	Total Cases	Total Tuberculous Empyemata	Per cent	Total Cases	Total Tuberculous Empyemata	Per cent
Group 1. Mechanically effective pneumothorax	346	24	7.0	45	0	0	163	7	4.0	138	17	12.0
Group 2. Mechanically ineffective pneumothorax	130	35	27.0	6	0	0	40	9	22.5	84	26	31.0
Totals	476	59	12.4	51	0	0	203	16	8.0	222	43	22.0

Group 1: The number of empyemata in this group was relatively small (table 1). There is a rather striking coincidence when the stage II cases are compared to Dufault's and Laroche's (2) report of finding 7 cases, or 5 per cent, empyemata in 138 mechanically effective pneumothoraces in a series of cases from 1932 to 1934, all of which were in stage II.

Group 2: There were 130 cases in this group of which 35, or 27 per cent, developed empyema as compared with 7 per cent found in group 1, a ratio of 4 to 1. This does not coincide with Matson's (3) statement that pure tuberculous empyema occurs with constant frequency irrespective of the type of collapse obtained. Forty were classified as stage II and, of these, 9, or 22.5 per cent, were complicated by empyema.

[2] Dr. Frank H. Washburn, Consulting Surgeon, Rutland State Sanatorium.

This is a definite increase when compared to the stage II cases in group 1 where only 4 per cent were demonstrated, a ratio of 5.5 to 1. The 84 cases falling in stage III were complicated by 26, or 31 per cent, purulent effusions as compared to 12 per cent in group 1 giving a ratio of 2.5 to 1.

Analysis of the 59 empyemata yielded the following data. The approximate time of onset of the pus in the pleural cavity after the induction of pneumothorax was in group 1 from three to fifty-three months, averaging 17.7 months and in group 2 from one to thirty-two months, averaging 11.3 months. Therefore, if an empyema is going to develop we may expect it somewhat sooner in the ineffective pneumothorax group as compared to the effective ones. The interval in months between the induction of pneumothorax and the appearance of empyema does not

TABLE 2

INTERVAL IN MONTHS BETWEEN INDUCTION OF PNEUMOTHORAX AND APPEARANCE OF EMPYEMA	NUMBER OF CASES	
	Group 1	Group 2
0– 3 months	0	3
4– 7 months	7	10
8–11 months	5	8
1– 2 years	6	10
2– 3 years	1	4
3– 4 years	3	0
4– 5 years	2	0
Total.....	24	35

differ materially in the two groups as is evident from table 2. Obviously since the good pneumothorax is maintained for a greater length of time the chances of purulent effusion developing are also apparent in this table. The duration of the empyema ran from two to eighteen months in both groups, giving an average of 6.3 months.

TREATMENT

The general method of treatment was to aspirate as much of the purulent fluid as possible and then irrigate the pleural cavity with warm physiological saline until the returns were clear. In one patient where response to this treatment was poor, a costectomy was done as a last resort measure. His elevated temperatures and toxaemia persisted. When the resected rib was examined the pleura was heavily infected and thickened, measuring 0.9 cm. and the subsequent course of the case

clearly demonstrated that it was this factor that was responsible for the toxaemic condition of the patient. When a situation like this is suspected, costectomy is of little or no value for absorption continues from the infected pleura. Alexander (4) strongly advises against costectomy in pure purulent tuberculous effusions.

RESULTS

Group 1 (24 cases): Seventeen had unreëxpanded lungs. Of these, 4 died, one from right-sided cardiac failure, 2 from pulmonary insufficiency and one from renal amyloidosis; 2 of the patients who died had a spread to the contralateral lung. Two were unimproved and had spread to the other lung. Four were improved. Six were quiescent, one of whom came to thoracoplasty. One case was apparently arrested.

Seven had reëxpanded lungs. Of these, 3 were unimproved, 2 showing spread. Two were improved, one quiescent and one apparently arrested.

Group 2 (35 cases): Of the 19 unreëxpanded cases, 7 died, 6 of pulmonary insufficiency and one of right-sided heart failure following costectomy. Four were unimproved, 3 of whom showed spread to the contralateral lung. Two were quiescent and one was classified as arrested. Five were improved, one of whom came to thoracoplasty. Of the 16 reëxpanded cases one died of pulmonary insufficiency, 3 were unimproved, 2 of which had spread to the other lung, 11 were improved or quiescent, of which 5 came to thoracoplasty. One was apparently arrested.

An interesting fact comes to light when the mortality rate in all patients with unreëxpanded lungs is compared to that with reëxpanded ones. There were 11 deaths in the 36 unreëxpanded cases, or 31 per cent, while in the 23 cases with reëxpanded lungs only 2 deaths occurred, or 8 per cent. Obviously then, those in whom the lung reëxpanded obliterating the empyema cavity did vastly better. All the above 13 deaths occurred in stage III cases, thus showing to what extent the mortality rate is influenced by the amount of lesions in the lungs.

COMMENT

From the above data it would be advisable to discontinue ineffective pneumothoraces that are producing no clinical improvement. In those where mechanical ineffectiveness is apparent but symptomatic relief is being obtained it is necessary to weigh the beneficial effects of the pneumothorax against the possibility of empyema and another later complication, amyloid disease.

In the presence of empyema the mechanically effective collapse should be maintained as long as the sputum remains negative or until it is considered safe to reëxpand the lung. If sputum turns positive, re-expansion should be hastened and thoracoplasty substituted.

SUMMARY

1. The incidence of pure tuberculous empyema in pneumothorax cases is definitely influenced by the mechanical effectiveness of the pneumothorax and by the amount of disease in the lungs (that is, the stage of disease).

2. In the series of 476 pneumothorax cases, 59, or 12.4 per cent, developed empyemata.

3. Empyema occurred four times as often in the mechanically ineffective pneumothorax cases as in the effective ones.

4. In stage II cases it occurred five and a half times as frequently in mechanically poor pneumothoraces as in mechanically good ones.

5. In stage III cases it was found two and one half times as often in mechanically ineffective as in effective collapse.

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LAMINAGRAPHY IN CHEST CONDITIONS[1, 2]

WILLIAM H. WEIDMAN AND JEAN KIEFFER

The value of laminagraphy in general has already been demonstrated by various authors. To date, however, the published accounts of its application to chest conditions have consisted almost entirely of case reports. This is unfortunate, for a distorted picture has necessarily been presented in which the spectacular results have been emphasized while the failures have been ignored. This study was undertaken to compare the results obtained by laminagraphy with those of the other roentgenological diagnostic procedures. Since information is the desirable end of any X-ray investigation, the method by which it is obtained is immaterial. Furthermore, this information must be useful, in some way influencing the treatment of the case under question. The usefulness of information obtained by the various X-ray techniques has, therefore, been of primary consideration in judging the results.

Each laminagraphic series was preceded by conventional stereoscopic films, a fluoroscopic examination and an overexposed posteroanterior film using a Lysholm grid. A horizontal Bucky film with the patient in a supine position was taken as part of every study and, when deemed necessary, lateral films were also made. In a few cases the results obtained by rectilinear and circular laminagraphic motions were compared with those of spiral motion. The latter, the parabolic spiral motion embodied in the laminagraph of Kieffer, was used as a matter of routine in all cases. When considered advisable, lateral laminagrams of the chest using spiral motion were also taken. To date, comparison with the high speed vertical Bucky has not been made, although the installation of additional equipment will make such studies possible in the near future.

After this system had been in operation for a short time, it was found that fluoroscopic examination gave meagre information in most cases.

[1] From the Norwich State Tuberculosis Sanatorium (Uncas-on-Thames), Norwich, Connecticut.

[2] Presented at a session of the Medical Section at the 35th annual meeting of the American Trudeau Society, Cleveland, Ohio, June 4, 1940.

It was therefore discontinued as an integral part of this study, chiefly because of the danger of excessive X-ray exposure. The average laminagraphic study of from seven to ten exposures, requiring 300 to 400 MAS at 90 cm. (35 inches), remains well within a safe X-ray dosage. However, if a lengthy fluoroscopic study is combined with a lengthy laminagraphic study, the margin of safety can easily be passed. At the average voltage used for this work, total exposure to the radiation should be kept below 3,000 MAS at three feet, or its equivalent, for any six-month period. This approximates 200 R units with a 1 mm. aluminum filter which must always be used.

Laminagrams were at first taken on 14″ x 17″ films. However, this size film was found to be unnecessary, except in a very few cases; 10″ x 12″ films and, in some instances, 8″ x 10″ films proved more satisfactory. The increased diagnostic value obtainable by the better elimination of secondary radiation and the reduced cost of the smaller films materially influenced this choice.

During the earlier part of the study laminagrams were taken 2 cm. apart. This distance proved too great in most cases and therefore was reduced to 1.5 cm. In some instances, particularly in apical studies, even this spacing proved too great, for much valuable information was missed. Consequently, level differences of 1 cm. were used in all apical studies. With the parabolic spiral motion nothing is gained by taking levels less than 1 cm. apart and in many cases 1.5 cm. is entirely satisfactory.

Most information was derived from a study of the posterior three-quarters of the chest and, consequently, laminagrams were taken with the patient in a supine position. With lesions near the film, less magnification is evident and, besides, the supine position is more comfortable for the patient. However, in cases where lesions are situated in the anterior quarter of the chest more satisfactory films can be obtained with the patient in a prone position. It is felt that with moderate respiration there is less vertical displacement of lung structure in the supine than in the prone position.

In any discussion of sectional roentgenography it is important to stress the necessity of coöperation between the roentgenologist and the technician, as well as the value of a rigid darkroom technique. Too often the diagnostic value of laminagrams is destroyed by improper X-ray exposure and faulty film processing. It was found that a horizontal Bucky film taken and developed before proceding with the laminagrams

was helpful because an estimate of the laminagraphic technique to be used could be made and proper centring of the patient could be noted. Furthermore, the information obtained by this type of film either aided in the interpretation of the laminagrams or supplanted them.

A scouting laminagram was then taken at the level most likely to show the desired part. In routine cases this scouting laminagram was normally taken at 1 cm. less than one-half the anteroposterior chest diameter. The film was then developed and the correctness of the technique estimated. In most instances this shows the bifurcation of the trachea. The series was then taken after making any necessary change in technique. Three central films were taken at levels 1 cm. apart and the remainder at levels 1.5 cm. apart, extending roughly between 4 or 5 cm. posteriorly and 13 or 14 cm. anteriorly. It is essential that the films all be processed similarly because any difference in densities in the films of any series will markedly decrease their informative values.

The number of films necessary to obtain optimum information varies with each case. The anteroposterior diameter of the chest, the location of the lesion, whether in the apex or base and deformities of the thoracic cage are factors which influence the number of films required. An apical study requires three to four films. Routine apical studies using four 8″ x 10″ films taken at 1 cm. intervals and located to include the apex have proved satisfactory. The contralateral apex can also be investigated on this size film and, frequently, unsuspected cavities are discovered. An average laminagraphic study of a thoracoplasty case requires about seven films.[3] In most cases eight or nine laminagrams were taken, purposely going beyond the useful range, and it was found that, as a rule, laminagrams taken below the 5 cm. or above the 14 cm. levels have little value. This is particularly true in thoracoplasty cases. The altered contour of the chest wall of the treated side markedly diminishes its anteroposterior diameter, and the anterior ribs are usually visualized between the 11 cm. and 13 cm. levels.

Varying target-film distances were used at first but, as a distance of 90 cm. was found the most satisfactory, it was soon used routinely. The kilovoltage and the milliampere-seconds used varied, depending on the position of the patient and the type and location of the area to be visualized. For apical studies and adhesions 40 MAS (10 MA, 4 seconds) were used, the KVP varying from 52 to 62; for thoracoplasty cases 40

[3] For a 20 cm. chest, the central laminagram is taken at 9 cm. and the entire series consists of the 5, 6.5, 8, 9, 10, 11.5 and 13 cm. levels.

MAS (10 MA, 4 seconds) at from 60 to 82 KVP; and for lateral laminagrams from 80 to 160 MAS (20 MA, 4 to 8 seconds), the general technique for the chest thus varying from 40 to 160 MAS and from 52 to 82 KVP. All these techniques are well within the range of the Machlett Type "A" tube which was used in this study (1.5 mm. target size). It is felt that the use of a larger target size or of a rotating anode tube is unnecessary.

The taking of a scouting film to judge the proper technique is still considered essential because it is almost impossible to definitely standardize laminagraphic technique except for broad, general groups. For example, the technique used in the study of thoracoplasty cases is necessarily vastly different from that used in an attempt to demonstrate adhesions in pneumothorax cases. It has been quite noticeable that there is less latitude in obtaining a satisfactory laminagram than in obtaining a satisfactory conventional film and that an exacting technique is necessary for optimum results. For these reasons, close coöperation between the diagnostician and the technician is demanded.

In sectional roentgenography of the chest it must always be remembered that the position of the material dealt with is altered by respiration. The depth of the respiratory phase during which the exposures are made must be contolled and duplicated as closely as possible because respiration alters the distance of structures from the focal plane. Some failures of technique can be definitely traced to lack of proper respiratory control. The best practical results were obtained by instructing the patient to breathe normally and quietly and then to hold his breath. No attention was paid to the slight degree of inspiration or expiration which might be present as long as the patient remained motionless during the exposure. It proved more difficult to duplicate results when the films were taken at full inspiration or expiration. Another factor which makes exposures at these respiratory phases inadvisable is that at full inspiration the differences of density between aërated lung fields and other structures is so great that it is impossible to obtain adequate visualization through the dense structures and in the aërated lung fields at the same time. At the normal depth of respiration both fields can usually be adequately visualized at the same time, while at full expiration the contrast is usually too low for best results.

The position of the head is another important factor. It must remain stationary and preferably in the median position throughout the entire series. A slight twisting to either side will markedly affect the position of the structures in the upper third of the chest.

The interpretation of laminagrams presents a problem which can be

overcome with experience. The chief difficulty appears to be the apparent unfamiliarity of structures never before visualized. It is difficult at first to realize that planes of focus are visualized and that these planes are diagnostic for a depth of from 0.5 to 1.0 cm. only. For this reason, the sectional films should be viewed in the same sequence and orientation. The structures under question must be followed from plane to plane and frequent comparisons made with conventional films of the same date. This procedure is extremely important. For example, fenestration of regenerated bone following thoracoplasty, if not traced from plane to plane, may be mistaken for cavities within the lung itself.

If four laminagrams are made on one 14″ x 17″ film, they should be cut so that the different planes can be viewed in proper sequence and orientation. It is unwise to view them otherwise.

It is well to remember that structures in the plane of focus are sharply defined and are blurred when out of focus. Cavities in focus have sharply defined borders, whereas when they are out of focus they appear as areas of increased density in the same relative position. This is true in the spiral motion but is not always true when the rectilinear motion is used. With rectilinear motion a cavity not in focus may appear as a longitudinal streak of increased density.[4] Small cavities with diameters of 1 cm. or less usually appear on one plane, whereas larger cavities are always present on two planes.

It is sometimes impossible to be definite about the presence or absence of tuberculous cavitation. The laminagraph will almost always demonstrate a cavity,[5] if present. However, identification of the type of cavity, that is, whether it is due to tuberculous cavitation, or a cyst, or an emphysematous bulla, *etc.*, is a question of diagnosis. When cavity walls are distinct, due to atelectatic lung tissue, inflammatory reaction or fibrosis, a definite opinion as to the presence of tuberculous cavitation seems reasonable. When the walls are thin and situated in the extreme apex, it is impossible to exclude the presence of an emphysematous bulla. The differentiation between tuberculous cavitation and an emphysma-

[4] A full discussion of the relative values of various motions is beyond the scope of this paper. The comparisons made between the various laminagraphic motions convinced us that the parabolic spiral motion embodied in the laminagraph of Kieffer produced more satisfactory results than those obtained with any other motion. In some cases the rectilinear motion gave false shadows difficult in interpretation.

[5] The term cavity is here used in the sense of physical cavity, a hollow place, a space devoid of anatomical structures. The use of the single word "cavity" to denote a tuberculous cavity is ambiguous and leads to much useless discussion.

tous bulla is difficult and at times impossible, chiefly because of inexperience in the interpretation of laminagrams. As more laminagraphic studies are compared with pathological specimens a more definite opinion in some cases may be warranted. The important point is that the laminagraph makes possible a roentgenological differentiation which heretofore has been impossible.

It must be acknowledged that there are certain limitations to laminagraphic techniques. This is particularly true in lateral laminagrams of the chest and in other cases where the high kilovoltage necessary results in films of low contrast. This often leads to difficulties in the interpretation of structures of low density.

Another problem which arises is the type of case to be laminagraphed. This procedure cannot be used indiscriminately, chiefly because of the expense involved. It is valuable in chest conditions showing atypical changes, investigation of mediastinal lesions and for definition of the trachea and bronchi. It is valuable in the investigation of the tuberculous lung in patients with a persistently positive sputum from an apparently unexplained source; in patients in whom there is question of collapse therapy, depending upon the presence or absence of tuberculous cavities and adhesions; in patients in whom the exact localization of apical tuberculous cavities is important before surgical intervention. It is most valuable in the visualization of the collapsed lung after thoracoplasty.

Included in this study are a hundred consecutive cases using our latest established laminagraphic technique. The results of the earlier experimental techniques were too inconsistent to be included. The following conditions have been investigated: tuberculous cavities, both apical and hilar; bronchial stenosis and occlusion; atelectasis; bronchopleural fistulae; tumors of the lung and mediastinum; lung abscesses; bronchiectasis; cystic disease of the lung; lung fields obscured by effusion, thickened pleura or oleothorax; adhesions and the collapsed lung in pneumothorax; paraffin packs and thoracoplasties.

In determining the presence of apical cavities the overexposed Lysholm and horizontal Bucky techniques are of value. However, even with these conventional techniques the clavicle and other bony structures frequently obscure the apical lung field. In most cases the laminagram facilitates the visualization of this portion of the lung. The presence of cavities in or near the hilum is another source of error when conventional techniques are depended upon exclusively. Occasionally, small cavities

situated in the subapical region of the lower lobes are obscured by the hilum, and in these cases laminagraphy is of great value.

With an adequate laminagraphic technique it is possible to visualize the trachea, its bifurcation and the upper and lower lobe bronchi. The more distal branches are not always delineated, their visualization being more or less fortuitous. Upper lobe bronchi, as a rule, are clearly defined and frequently more information can be obtained by laminagraphy than by bronchoscopy. It is well to remember that the lateral margins of the trachea and bronchi are sharply defined when a patient is in the supine position, whereas the anterior and posterior aspects are shown to better advantage by the lateral technique. Some of the more spectacular results in laminagraphy are obtained by the demonstration of tumor masses occluding or distorting the trachea and bronchi.

In the tuberculous patient, laminagraphy of the bronchi gives much interesting information. Although an insufficient number of pneumothorax cases have been studied to arrive at definite conclusions, nevertheless, there are suggestions of a correlation between the failure of cavity closure and partially occluded bronchi.

Two cases of tracheobronchial ulceration were diagnosed previous to and confirmed by bronchoscopy.

In cases of massive atelectasis, cavities and bronchiectasis-like cavities are seen to better advantage than with the conventional film. In partial atelectasis the extent of involvement can usually be accurately defined.

If the fistulous opening of a bronchopleural fistula is not too small nor too tortuous it can be demonstrated without the use of an opaque medium. Of course, the visualization of fistulae is somewhat problematical. It must be understood that if insufficient sections are taken, or if the sections are too far apart, small fistulae may be missed. However, the technique suggested earlier has proved satisfactory.

Laminagraphy provides an exact means for the localization of lung abscesses. In those cases in which the abscess cannot be localized by opaque media, laminagraphy is indispensable. It is important that sections be taken beyond the existing lesion, otherwise the results may be inaccurate. One failure in this series was attributed to this neglect.

The distal branches of the left lower lobe bronchus are more difficult to visualize than those of the other bronchi because of the cardiac shadow. The density of the cardiac muscle necessitates the use of a higher kilovoltage. This higher kilovoltage may be unsatisfactory for the visualization of the lung field lateral to the heart. Laminagraphy has proved

superior to conventional methods when an opaque medium is used to demonstrate bronchiectasis if there is an occlusion of the involved bronchi above the bronchiectatic changes.

Laminagraphy has proved invaluable in the investigation of the lung parenchyma obscured by an effusion, thickened pleura or oleothorax. It is particularly useful in definitely localizing encapsulated effusions.

It has proved very useful in pneumothorax cases for the demonstration of adhesions and cavity formation. It is surprising to find persistent cavity formation in an apparently satisfactorily collapsed lung. The conventional techniques have not proved entirely satisfactory for the visualization of partially or completely collapsed lung parenchyma.

In tuberculous patients considered candidates for paraffin pack, laminagraphic study previous to the operation accurately localizes cavity formation so that the surgical problem is greatly simplified. After the paraffin is in position laminagraphy is the only satisfactory means available for visualization of the obscured lung field.

X-ray examinations of the chest in patients with thoracoplasty using the conventional technique have, in the past, proved unsatisfactory. In a patient standing in a posteroanterior position a torsion of the chest is evident. There is usually a scoliosis of the dorsal vertebrae and the sternum is not in the central position. This can partially be corrected by the use of an anteroposterior position, that is, with the patient facing the X-ray tube. By this means more of the collapsed lung is visible. However, the depth of the lung field is too great and its width too narrow for proper visualization by this means. Furthermore, the presence of regenerated bone greatly interferes with the interpretation of the film. The best single means of visualization of the lung other than that obtainable by the laminagraph has been found to be a horizontal Bucky of good quality with the patient in a supine position. The spine in this position is straight and there is no interfering scoliosis.

The use of the laminagraph in investigation of thoracoplasty cases is felt to be not only invaluable but indispensable. The scapula in its relation to the ribs can be demonstrated clearly and the position of the remainder of the scapula after scapulectomy can be seen clearly. All the regenerated bony structures of the distorted thoracic cage can be followed accurately. This is felt to be an extremely important diagnostic possibility. The periostial bed in which bone regeneration has been artificially prevented can be seen and any fistulous opening demonstrated. The borders of the apical pleura can be completely followed after an

apicolysis has been done. If an adequate laminagraphic technique is used the entire compressed lung can be seen.

In partial thoracoplasty, progression of tuberculous infiltration has been discovered extending into the anterior portion of the upper lobe or below the area of compression. If the compression of lesions situated in the right apex is not satisfactory below the lower margin of the upper lobe, frequently cavities eventually develop in the lower and anterior portions of the upper lobe.

In complete thoracoplasties the collapse is usually quite satisfactory posteriorly, but is less effective anteriorly and in the midsections. It has been clearly demonstrated that costal cartilages are relatively wide and considerable lung tissue remains uncollapsed providing it has not been replaced by herniated lung from the contralateral side. A herniation of the contralateral lung well across the midline is quite frequent in complete thoracoplasties. This fact was completely unsuspected previous to undertaking this study. A distortion of the bronchi on the operative side is a frequent and expected finding. Occlusion of the smaller bronchi may occur producing small bronchiectatic cavities in an atelectatic lung. These bronchiectatic changes appear to be more frequent in those cases in which the lung was atelectatic prior to thoracoplasty.

The extent of tuberculous empyemata can readily be demonstrated without resorting to the use of an opaque medium. This is an important consideration, for opaque media cannot always clearly delineate the ramifications of these cavities. Fistulous openings situated between the intrapleural space and subcutaneous tissue can also be shown.

In comparing the relative value of laminagraphy and other available techniques it is extremely difficult to give a purely scientific and impartial opinion. In order to be impartial the values of the conventional techniques were estimated before comparing them with the laminagrams. It was noticed that the interpretation of films taken by one technique markedly influenced the interpretation of the others. For example, certain structures seen on a conventional film appeared more prominent in the horizontal Bucky film but still were not definite enough for diagnosis. However, after seeing the same structures clearly defined on a laminagram, a more definite opinion could be expressed by a revaluation of the conventional techniques. Because of this difficulty it was considered inadvisable to make an actual statistical comparison of the various methods employed.

It must be remembered that the purpose of any radiographic examination is to obtain diagnostic information beneficial to the patient rather than to prove the superiority of one technique over the others. Each technique has its own place and there are limitations to all. It is useless to compare results without giving due weight to the problems to which an answer is sought. If satisfactory information is obtained by one method, other methods are unnecessary. Furthermore, the type of lesion under question is an important consideration. For example, sectional roentgenography should not be depended upon in the diagnosis of early tuberculosis, and conventional techniques have definite limitations in the investigation of obscured lung fields.

In tabulating the results of the laminagrams according to their informative value, three broad groups were selected: (1) that in which no particular information could be obtained; (2) that in which the information derived was valuable but not entirely unsuspected; (3) that in which the information obtained was entirely unsuspected.

The first group, considered failures, consisted of 18 cases, or 18 per cent, of the 100 cases studied. The reasons for these failures were inexperience in interpretation, disregard of technical factors, such as improper X-ray exposure, or sections too wide and too few and, finally, definite technical limitations in the machine itself.

The second group, in which the information was valuable but not entirely unsuspected, consisted of 36 cases (36 per cent). The results in this group were difficult to judge, for here most difficulty was encountered in comparing the relative value of the techniques employed. It must be stated in all fairness to the laminagraphic technique that, had the conventional films not been of high quality, the group of "unsuspected" results would have been increased.

Finally, in 46 cases (46 per cent) the results were classified as "unsuspected information."

Included in this series were 44 random thoracoplasty cases, from various institutions, in which different operative techniques had been employed. In 40 of these (91 per cent) the laminagraphic study disclosed valuable information not obtained by any other means, and the information was entirely unsuspected in 25 (56 per cent). Four cases (9 per cent) were considered failures.

At the beginning of this study we were very much discouraged with some of the results; they often did not reach our expectations. This was found to be due mostly to an inadequate technique. All the diffi-

culties, however, were not technical, but some were due to faulty interpretation. It was surprising to see how much had originally been missed when some of the earlier films were later reviewed. After the technical limitations were overcome, practice in interpretation obtained and the limitations of the method definitely recognized, we found that laminagraphic studies gave a wealth of information besides the spectacular examples which everyone has already recognized. The results of this present study coupled with the review of work done at other institutions permits the assertion that with strict attention to detail the informative value of laminagrams is great enough to warrant their use as an established roentgenological diagnostic procedure.

CASE-FINDING IN TUBERCULOSIS[1]

ROBERT G. BLOCH

THE OBJECTIVE

Case-finding has become the watchword in the fight against tuberculosis. It means that we are trying to bring under medical observation and treatment tuberculous people who are unaware and unsuspected of having the disease. The treatment of the patient whose symptoms lead him to seek medical care has failed to solve the tuberculosis problem. The decreasing mortality during the past few decades proves itself to be largely the expression of an increasing immunity among the population and of the decreased infection hazard due to better isolation methods and to the closure of sources of infection by collapse therapy. It is not so much the result of curing pulmonary tuberculosis in hospitals and sanatoria. The statistics of Drolet (1) show a depressing constancy of the ratio of deaths to new cases of tuberculosis reported in various communities during the past twenty years. To quote a few of his figures, in New York City and State, in Detroit and Philadelphia, it decreased by 5 or 6 per cent, in New Jersey and Massachusetts, about 1 or 2 per cent, in Chicago, not at all. These are indeed negligible results in spite of improved institutional facilities and therapeutic advances. Every tuberculosis physician knows that the explanation is the persisting difficulty of really curing advanced tuberculosis; that its treatment is time-consuming and costly beyond the imagination of the patient and the public at large; that in spite of many satisfactory individual results, only relatively few such patients can be kept in institutions until they can be discharged with a maximum of safety. But even so, most of our institutions for the tuberculous are filled by a majority of patients with far advanced disease occupying the beds in which those with early tuberculosis could be cured in a comparatively short time. Hence, unless the institutional facilities are multiplied at a staggering cost, any attempt to increase hospital care for advanced tuberculosis in numbers and time would result in further reducing the chances of patients with minimal disease to regain their health.

[1] From the Department of Medicine, University of Chicago, Chicago, Illinois.

The obvious solution of the problem lies in minimizing the number of people with advanced tuberculosis, that is, in not permitting early tuberculous disease to progress to the advanced stages. If we add from the epidemiological point of view that the patient with open, cavernous and, therefore, advanced tuberculosis is the most important source of infection, it becomes ever so much clearer that the prevention of advanced tuberculosis means, in a practical sense, the prevention of tuberculosis.

The necessity of early diagnosis has been proclaimed for many years. Annual campaigns by way of picture posters and other means have appealed to men and women with certain symptoms to submit to medical examination. Cough, expectoration, haemoptysis, fever, night sweats, anorexia and loss of weight were called the "danger signals" of tuberculosis. In more recent years we have learned that they are not so much the danger signals of a threat as the expression of an already present calamity. In a previous publication (2) we wrote, "Early tuberculosis, that is, tuberculosis of minimal extent which has not advanced into the stage of tissue necrosis, rarely causes noticeable symptoms. An amazing number of people with extensive and occasionally spectacular disease do not have enough symptoms to arouse the suspicions of the patient himself, his family or even his physician." The assumption that the patient with early tuberculosis remains free of symptoms does not include all the clinical possibilities but is an excellent working basis for any efficient attempt to find early disease. Modern case-finding does not appeal to the man and woman in the street who already have the signs of illness; it actively searches among the seemingly healthy. Consequently, the National Tuberculosis Association has recently changed its campaigning for early diagnosis from the "symptoms-are-danger-signals" technique to the "don't-wait-until-you-feel-sick" method.

APPLICATION

The chief object of any preventive attack against tuberculosis and therefore, of any case-finding effort, has been, until very recently, and for many still is, the childhood age. The reason for this is, in part, probably the emotional preference for the child in all medical efforts, and to a greater extent the easy accessibility of large groups of children, but, essentially, the basic idea that it is the tuberculous infection during childhood which determines the fate of the individual with regard to tuberculosis. Without attempting here an academic discussion of vari-

ous viewpoints concerning the significance of primary infection, reinfection and superinfection during various age periods, the facts applying to case-finding are that much more tuberculosis of clinical significance is found in adults than in children. This includes children up to and beyond the threshold of adolescence. The experience of many investigators and his own have culminated in Plunkett's (3) simple statement that, "Pulmonary tuberculosis is a disease primarily of adults." Since children are peculiarly free even from small lesions which can be considered as capable of pathological development, it follows that the majority of the active tuberculous lesions in the lungs of adults develop after adolescence. The child, therefore, may be more prone to tuberculous infection than the adult but not to the development of destructive and life-threatening forms of chronic tuberculosis. That this experience is contrary to old beliefs is best expressed in some of our laws governing the health of the people. If, for example, the health regulations of the State of Illinois (4) place restrictions on the contact of infectious tuberculous persons with children up to the age of sixteen but not after that, it signifies that public officials have undertaken the absurd task of decreeing the date on which a person ceases to be endangered by the inoculation of the tubercle bacillus. There are no medical facts on which such rules could justly be based. Our own experience at the University of Chicago has convinced us that the overwhelming majority of such pulmonary tuberculosis is acquired by exogenous superinfection, mostly of young adults, through the intimate contact with open tuberculosis in domestic life. In a survey which we previously published on case-finding results throughout the world, it was shown that the incidence of clinically significant adult tuberculosis was more than 9 per cent among contacts, or three times as high as it was in the second most afflicted groups, the so-called racial groups and the unemployed of the United States, where it was found to be 3.2 per cent. There is close resemblance of the figures obtained in this country to those of Europe. It is essential that the weight of the evidence will more and more direct the assault against the tuberculosis problem by way of the adult rather than through the child. There is no better prevention for children as well as for adults than the elimination of sources of infection.

The soundness of this contention with reference to children can be illustrated from our own experience by the stories of several nursemaids with advanced and open tuberculosis who had moved from one family to another, presumably inoculating children with tubercle bacilli before

their disease was discovered. If the infants in their care had been examined at school age when most surveys in children are carried out, an interval of several years and of much possible pathological progress would have elapsed. But even if the children could have been examined soon after inoculation, negative findings may have indicated that this time they had escaped. But what about subsequent exposure to another nursemaid? the kindergarten teacher? the out-of-town relative who comes visiting? In other words, how often and up to what age should we examine children to safeguard them from tuberculous infection? The answer is that such examinations would have to be so frequent and extend through so many years as to make them technically and economically difficult, if not impossible. The obvious solution of the problem lies in the search for the distributors of the infection. If a maniac shoots wildly at the people of his neighborhood, the trouble is not eliminated by looking for bullet holes in the clothes of those who might have been hit, but by the apprehension of the culprit and the silencing of his gun!

Since only caseous—that is, potentially cavernous—and cavernous tuberculosis eliminate tubercle bacilli in appreciable numbers from the lung, and since approximately 85 per cent of all tuberculous infection is air-borne, it can be said, in short, that *the cavity in the lung of the adult is the main source of tuberculous infection.*

We may summarize by stating that case-finding among adults of all ages reveals the distributor and, by examination of his contacts, the recipient of the tubercle bacillus, that it therefore brings advanced as well as early tuberculosis under treatment and leads to the timely protection of the healthy by the possibility of isolation.

Probably more than half of the reports published on case-finding in adults concern themselves with university students, hospital personnel and student nurses, with a special interest in medical students. Consequently, a rather exaggerated impression of the importance of the tuberculosis problem among these groups has become widespread. Brahdy (5) points out that the incidence of tuberculosis among hospital personnel is about the same as that of any similar group. This coincides with the findings at the University of Chicago. We have had no experience with student nurses, in which Brahdy and others find an exceptionally high occurrence of the disease. Of course, the health problem of students and especially of medical students, as well as of hospital personnel, should be one of great concern in any medical school or institution and there should be no limit to protective measures

against the danger of tuberculosis. The zeal of the investigators at the University of Minnesota, under the leadership of Myers and Diehl (6, 7, 8, 9) has made institutional authorities everywhere acutely conscious of that problem. However, beyond the best attainable health protection, we of the medical profession will still incur unavoidable hazards which are the duty and privilege of our calling. The elimination or curtailment of the badly needed and widely neglected training of medical students and nurses in chest disease would be as little justified as their avoidance of contact with other and more acute infections. Certainly, the assumption that tuberculosis in universities and medical institutions is a public health concern of major proportions is erroneous. Measured against the problem in other groups of the population, it can be taken only as the preliminary of a great attack against the enemy's main positions. The student in medicine and nursing has been the fitting object of a study in the epidemiology of tuberculosis, but disproportionate emphasis on his problem is not justified.

Tuberculosis is found in all classes of the population. The well-to-do and the rich are by no means free of it. Consequently, thorough case-finding not only demands organized efforts by agencies concerning themselves with the health of the poor but, as Myers (10) and Douglas (11, 12) have pointed out, the active search for the disease by every physician in his private practice. However, the inseparable association of tuberculosis with poor and crowded living conditions makes the socially less privileged the obvious objective of the chief attack. It is not easy, and until recently was well nigh impossible in Chicago, to obtain access to a group of the adult population in the industries, the unions and in social centres who would be willing to take the risk of losing job and means of livelihood because of a possible diagnosis of tuberculosis.

After initiating case-finding programs among the students of the University of Chicago, the personnel of the University clinics, (2) and the expectant mothers reporting to the clinic of the Chicago Lying-In Hospital, (2, 13) a more ambitious project was begun at the clinic of the Provident Hospital of Chicago where an average of 16,000 Negroes are admitted annually. The initial results of that investigation will be reported elsewhere.

METHODS OF EXAMINATION

The significance which can be attached to the results from case-finding surveys depends upon the training and experience of the examiners, their concept of tuberculous disease resulting in varying interpretations of

pathological findings, and last but not least, upon the method of examination. If a group survey had been undertaken twenty-five years ago, it probably would have been done by physical examination of the chest. As a result, very little early tuberculosis, if any, would have been discovered and a great number of the more advanced cases would also have been missed. The inadequacy of the physical method in discovering pulmonary disease and inaccurately determining its extent is now an accepted fact. The attitude that the efficiency of the time-honored percussion and auscultation exceeds that of other diagnostic procedures betrays inexperience in the comparison of their respective values. I do not wish to be misunderstood. No medical diagnosis is ever complete without a thorough physical examination combined with all other available methods of diagnosis. Without physical examination our medical advice for treatment would lack the backbone which alone can make it stand. But medical diagnosis in the traditional sense of the word is not the topic of this discussion. Our problem is to recognize disease among large groups of people, to do so with the greatest possible speed and efficiency, and only then, to subject those who are found to be sick to further diagnostic procedure. For the purpose of case-finding in tuberculosis, the physical diagnosis can be considered as eliminated in favor of the tuberculin test and the X-ray examination.

A considerable part of the literature of the past few years has been occupied by controversy about the respective virtues and failures of either of these methods or the combinations of both. Myers (14) and his associates as well as others have been so enthusiastic about the diagnostic reliability of tuberculin that they have based their health programs almost entirely on its use. Indeed, tuberculin has been so widely heralded as the most potent discoverer of the disease that one should not expect it still to be the controversial subject which it is. The fascination by the biological phaenomena expressed in the manifestations of tuberculin, and the hope that some day through their full explanation the mystery of tuberculosis may be solved, seem to have exerted an influence on its practical present-day application. Space forbids going into the scientific aspect of the problem. For the purpose of case-finding, it is necessary to state that the positive tuberculin test *per se* expresses nothing but that an infection with the tubercle bacillus has taken place. The patient's age permits clinical conclusions only insofar as a small child has had insufficient time to build an immunity which could be commensurate with the allergic status expressed in a positive tuberculin test, especially if the reaction is strong.

The change from a negative to a positive test and from a weak to a strong reaction permits the conclusion that the infection status and subsequently, the allergic status has changed, but little else. In practice, these changes should evoke watchfulness for the possible development of a clinically significant tuberculosis but not be interpreted as proof that such a lesion is already present. Since a positive reaction frequently turns negative, and since the change from negative to positive and vice versa can repeat itself during the life span, it is not possible to say, as far as adults are concerned, whether a positive reaction expresses a primary or reinfection, and yet much attention has been given to the "primary infection in adults" on just that basis. The missing evidence of a previous infection in the X-ray film does not confirm the primary nature of a tuberculous allergy since the complete reabsorption of such lesions, or at least their elimination from X-ray visualization, occurs frequently. The absence of a lesion and a concurring negative test does not permit a reliable conclusion as to a person's tuberculous status in the past or even in the present. On the other hand, the presence of calcified foci does signify a past tuberculous infection in spite of a negative test. The discrepancy cannot be explained away by the assumption that calcification in the lung may be the residual of a nontuberculous involvement. All medical experience of the past points to the tuberculous nature of the overwhelming majority of calcified foci in the lungs.

One could enter into more arguments to illustrate the uncertainty which prevails concerning the value of tuberculin surveys. Lately, the enthusiasm for tuberculin seems to be abating and cautious statements have appeared about it. Experienced physicians active in Public Health have expressed dissatisfaction with the results obtained. Lumsden (15), McKneely (16) and Knies (17) have found the test unreliable. Long (18), a staunch believer in tuberculin and one of its foremost investigators, realizes "the confusion which still exists." That confusion seems to be due largely to an insufficiently sharp differentiation between the value of tuberculin in children and adults. The incidence of clinically significant pulmonary tuberculosis in small children is low and the tuberculin test is of sufficient reliability not to warrant the more costly X-ray surveys, whereas in adults, beginning with adolescence, the interpretation of the test is so involved that replacement by the X-ray method is indicated. Crimm, Potts and Hudson (20) recently have added new weight to the opinion that tuberculin is unreliable as an indicator of all past tuberculous infection. In a comparative study these authors found that "about 21 per cent of the individuals

with pulmonary lesions would have been overlooked" if the tuberculin test alone had been employed.

Tuberculin surveys are used only as a so-called screening method which has to be supplemented by X-ray examination of all positive reactors. In the adult population of urban, and especially of metropolitan areas, where the number of reactors is great and therefore the control by subsequent roentgenological examination is costly, the X-ray as the exclusive primary method of examination should be employed for reasons of economy, if for no other.

Of the various forms of roentgenological examination, each has its pros and cons. But all of them, if expertly applied, are superior to the tuberculin test in accuracy of diagnosis and in time saving. The disadvantage of the greater cost has been practically eliminated by the recent introduction of more economical procedures which should bring large scale surveys within the financial reach of any community.

In our own group examinations we have, as a screening method, always used fluoroscopy, the cost of which has from the beginning, been lower than that of the tuberculin test.

A technically good roentgen examination reveals the overwhelming majority of all clinically significant tuberculosis in the lung. The similarity of shadows cast by blood vessels with those of tuberculous foci and a few other errors of past years are now too well known to be a serious obstacle to correct interpretation. Much has been written about the importance of finding calcifications. The recognition of calcified foci is of great epidemiological interest but of little concern in a practical case-finding program.

There is a definite limitation to the size and opacity of a lesion which can be demonstrated. Isolated tiny fresh tubercles are not registered by the average X-ray picture; furthermore, tracheobronchial lymph node disease may be obscured by the mediastinal structures. However, the major object of the examination is attained if the larger areas of infiltration are discovered. Among those can be included even the minimal involvements of little size and radio-opacity. The presence of all more advanced disease can be recognized almost at a glance, although prolonged inspection may be needed for a pathological appraisal. With each step from stereoscopic transparent films to the less expensive techniques, the accuracy of demonstration and interpretation will necessarily suffer. The single transparent film, the miniature fluorogram which was introduced recently (19), and the paper film, in the order named, each

seem to be somewhat less reliable than the previous one, but all of them will reveal enough to the experienced eye to give satisfactory results in large scale surveys.

It was with apprehension that we began our own group examinations by using fluoroscopy, supplemented by roentgenograms in all cases of definite and suspected findings. This technique was dictated to us by economy. However, from surveys in which over 20,000 persons were examined by our group, we have become convinced that fluoroscopy is a wholly satisfactory method and therefore are willing to retain it regardless of whatever funds may be available. There is good reason to believe that very few of even small parenchymal infiltrations are overlooked by an experienced examiner who is well trained in fluoroscopic technique, in roentgen diagnosis and in pulmonary pathology. Most of the critics of the fluoroscopic method with whom we have had personal contact betrayed a considerable lack of these requirements and offered opinions on the subject which originated either from hearsay or from an apprehension of the unknown.

Fluoroscopy offers the advantage of looking at the living chest, of seeing not only anatomical and pathological detail, but to some extent, physiological manifestations such as the function of the diaphragm, not to speak of a number of observations on the cardiovascular system. It permits the change of the patient's position when this seems indicated as, for example, when mediastinal involvement is suspected.

The disadvantages of the method are the absence of a permanent roentgenographic record, the reliance on one physician's opinion which he has to form in a very short time and the limitations of the examiner's endurance. After the fluoroscopy of 60 to 70 patients, fatigue interferes with accurate observation. This necessitates teamwork of several physicians when large groups are examined within a short period of time.

All of the methods of X-ray examination need to be further improved for the special purpose of mass application. The question as to which is the most suitable will be decided by technical advances and by the requirements in different localities.

With the increased interest of authorities and of the public, the number of case-finding surveys can be expected to increase rapidly. There is hope that group surveys on an ever increasing scale will be organized throughout the country and that we are not far from the day when laws and regulations will make an X-ray examination of the

chest a prerequisite for employment in domestic service, in the teaching professions, in industry, in the fighting forces and for the issue of a marriage license. It appears that we have a weapon in the fight against tuberculosis which, without any spectacular advance in scientific research, can carry us far towards the elimination of the disease as a major public health menace.

SUMMARY

1. The search for unsuspected pulmonary tuberculosis has become one of the major public health activities.

2. Open tuberculosis in adults is the main source of infection.

3. The best opportunity of early diagnosis and prevention of the disease in adults lies in the discovery and elimination of advanced tuberculosis.

4. Equally, the most efficient approach to the tuberculosis problem in children is through the adult population.

5. The tuberculin test as a method for surveys among the adult population is inferior to X-ray examination.

6. Fluoroscopy by experienced examiners and supplemented by X-ray pictures is a reliable method for finding pulmonary tuberculosis.

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DECLINE OF TUBERCULOSIS[1,2]

Present Death Rates and the Outlook for the Future

LOUIS I. DUBLIN

In a series of papers and addresses made over a period of nearly twenty years, I have been stressing two principal points in the analysis of the problem of the control of tuberculosis. First, I have attempted to evaluate the various forces which have been at work to bring the death rate from tuberculosis under control. The emphasis has been throughout that tuberculosis is primarily a communicable disease and that the most effective approach from the public health officers' standpoint is like that toward any other communicable disease, namely, to break the chain of infection. There is to-day no one with authority in either the field of public health or of medicine, who would question this conclusion. Time has completely confirmed the thesis that the attack must be on the environment, however important the genetic factors may be in our understanding of the natural history of the disease. The problem of the health officer and of the medical attendant is to discover cases of tuberculosis, to isolate those that are infectious, to teach the patients how to take care of themselves and how to avoid infecting others, to attempt to arrest the disease through appropriate medical treatment and, most important of all, to help raise the general health of the population to increase resistance against the infecting organisms. This program is now universally accepted and is in practical operation in an ever-increasing number of American states and cities. The old controversy engendered by Karl Pearson in England thirty years ago, as to the importance of the genetic factors is now as dead as the dodo. Time has proved that our old friend Arthur Newsholme was right.

My second effort has been to encourage the belief that the disease can be eradicated, if not entirely, at least to the point where it would be a minor item in the list of causes of death. As you know, there have been, these last twenty years, distinct indications that the disease, in

[1] Presented at a session of the Administrative Section of the 36th annual meeting of the National Tuberculosis Association, Cleveland, Ohio, June 4, 1940.

[2] Metropolitan Life Insurance Company, New York City.

certain favorable groups at least, was rapidly approaching a point where we could see virtual eradication very much in sight. On the basis of this experience and considering the trend of the death rate for a series of recent years, I attempted to make a forecast. Some of you will remember my expectation that if the forces directed against tuberculosis were actively continued, the death rate from tuberculosis could be reduced to below 40 per 100,000 by the year 1940, and that before very long thereafter we would arrive at a point where there was substantial eradication of the disease as a public health problem. These forecasts have been, on the whole, received by some workers in the field with a certain amount of incredulity and in all frankness, I must say that I was over-optimistic. Yet, as a matter of fact, the last two decades have not been years of unsatisfactory progress in the campaign against tuberculosis. The indications are very good that the year 1940 will show a death rate for the whole country of the order of 45 per 100,000, or even less. In the current year, not less than eleven states, I believe, will show rates of less than 30 per 100,000. It is a matter of some interest that for the white population of the United States, the rate this year will be appreciably lower than the figure which I had assumed for the population as a whole. If, in other words, my forecast had been made to apply to whites, it would have been too conservative. The death rate for whites is now the lowest recorded for any country in the world. If I did not quite succeed fifteen or twenty years ago in foreseeing the exact rate for 1940, it was perhaps because at that time it was impossible to give sufficient weight to the resistance which the disease has shown to our feeble efforts to control it in those particular groups and areas where it was most solidly entrenched, namely, among the colored, in certain occupations and in a few less active states where the disease is still a matter of considerable public health importance.

Let us see what the situation actually is in the various geographic areas and in the several groups of our population. As I have already said, the death rate this year will in all probability be under 45 per 100,000. This will represent a decline of over 37 per cent in the last ten years and of 61 per cent in the last twenty. The average annual rate of decline has been 3 per 100,000, or about 4.2 per cent of the average rate of the period during the last eighteen years. This is a pretty fair indication of the vigor of the movement to control tuberculosis. Even more impressive is the situation in the rural section of the country. Among the 57,000,000 residents of these areas, we estimate the rate to

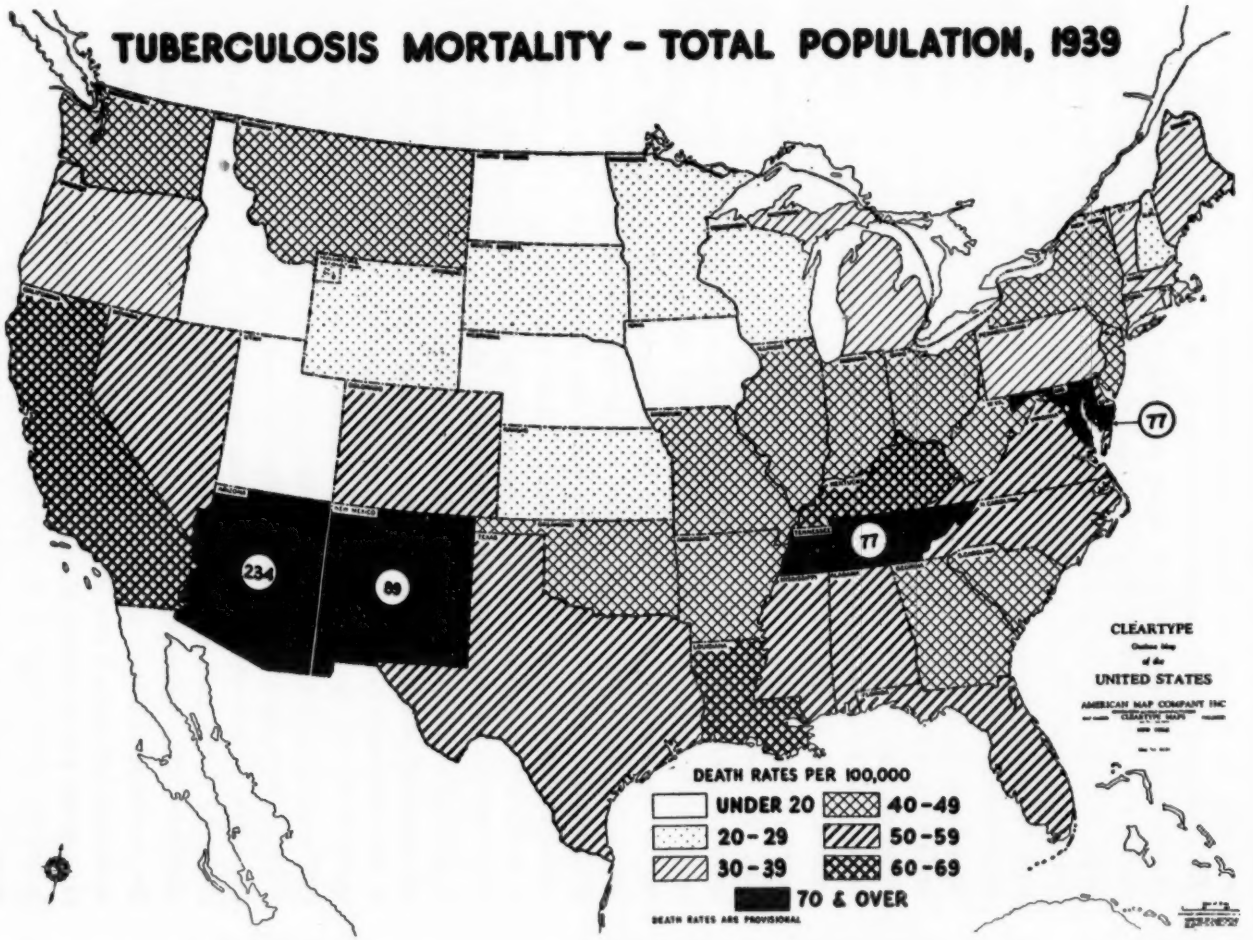
TUBERCULOSIS MORTALITY - TOTAL POPULATION, 1939
234
80
77
77
DEATH RATES PER 100,000
UNDER 20
20-29
30-39
40-49
50-59
60-69
70 & OVER
DEATH RATES ARE PROVISIONAL
CLEARTYPE
UNITED STATES
AMERICAN MAP COMPANY INC

CHART 1

be slightly over 40 per 100,000. In rural New York last year, the resident rate was only 25.7 per 100,000. If the total rural rate still runs high, it is largely because of the effect of the high rates among rural Negroes.

To visualize our problem more definitely, I have produced a map which shows the death rates from tuberculosis in the year 1939 in the various states of the nation (chart 1). It is a matter of interest that for five of the forty-eight states, the death rates were under 20 per 100,000 and for six more, they were under 30. These are, for the most part, rural states, but together they account for 15,000,000 people. Eight additional states show rates between 30 and 40; 12 with rates 40 to 50. Only seven states had rates in excess of 60, namely, California, Kentucky, Louisiana, Maryland, Tennessee, Arizona and New Mexico.

Nor must we suppose that the improvement in the tuberculosis situation has been limited to the rural areas. The rate of decline in the urban centres of the population is very much the same as in the country as a whole. There are, furthermore, large cities such as Rochester and Syracuse in New York, St. Paul and Minneapolis, Minnesota, and quite a number of others where the rate has been reduced to between 30 and 40 per 100,000. Even among the more than seven million white residents of New York City, the rate has been reduced to about 39 per 100,000.

CHART 1

Let us now examine the tuberculosis picture with reference to color, sex and the age groups of our population. We may get some directive clues thereby. The large colored population constitutes our chief reservoir of tuberculosis and it is among them that the bulk of our preventive and curative effort must be directed. We shall never succeed in achieving our objectives until we take more seriously than we have in the past the problem of eradicating tuberculosis among them. The fate of the whites, as well as of the colored, is involved in this effort. In 1938, which is the last year for which figures by color are available, the death rate from tuberculosis among the colored was 135.2 per 100,000, in contrast with a rate of 39.0 for the whites. In other words, the rate for the colored was about three and one-half times that for the whites. This does not mean that the colored population has not made much progress in the control of tuberculosis. The rate for 1938 represents a decline of 38 per cent in the last ten-year period and of 45 per cent in the last seventeen-year period. The colored people have not yet advanced beyond the position of the white population in 1910.

The rates for the colored vary in the several parts of the country as

do those for whites, the highest Negro rate in states with sizable Negro populations being recorded in New York and the lowest in Arkansas. Much depends upon the proportion of rural to urban population, for it is in the cities that the death rate for the colored rises to its highest proportions. The mortality from tuberculosis among city Negroes is roughly twice that among rural Negroes. As a general rule, the urban Negro succumbs to tuberculosis at a rate four to five times that of city dwelling whites. There are many cities in which the disparity is even greater. For example, in Newark, New Jersey, the white rate in 1938 was 37 as against a rate of 325 for the colored. In Cincinnati, the rate for whites was 54, while the rate for the colored was 301. In Milwaukee, it was more than eleven times as high, the rate for the whites being 42 and that for the colored 485. Analyzing our problem further, we find that it is especially among young colored people that this excessive mortality is concentrated. In the ages under ten, the rate is from four to five times as high as among the whites, and among colored girls between ten and fourteen, it is about nine times as high. One need hardly labor a situation as terrible as that. The condition cries out for correction. We cannot say we are serious about the tuberculosis problem in the United States until we make every effort to correct this situation among our thirteen million colored people.

Let us now examine the problem of tuberculosis in the two sexes and also in the various age periods of life. The latest figures available in such detail are for 1938, but chart 2 shows very clearly a situation which I believe, in its essentials, reflects the current status. A most interesting fact is that among whites between the ages of five and fourteen, rates as low as 3 per 100,000 are found. We can say that among white children of school age tuberculosis is no longer a problem of mortality, although there are, of course, sizable numbers of reported cases among such children. You will see from the chart that among white males the rate reaches its maximum after age sixty-five, when it is 106 per 100,000 and stays close to this maximum thereafter. Among white females, on the other hand, there are two peaks; one of 46 which is reached at the age period twenty-five to thirty-four, and a later one after age sixty. There is a broad plateau of fairly high mortality in the main childbearing ages. This fact is also clearly shown in such reports of cases as we have. We find a concentration of cases at these same ages among women and these, of course, represent only a fraction of the total cases which could be found if an attempt were made to gather them all.

TUBERCULOSIS MORTALITY BY AGE, RACE & SEX
UNITED STATES, 1938

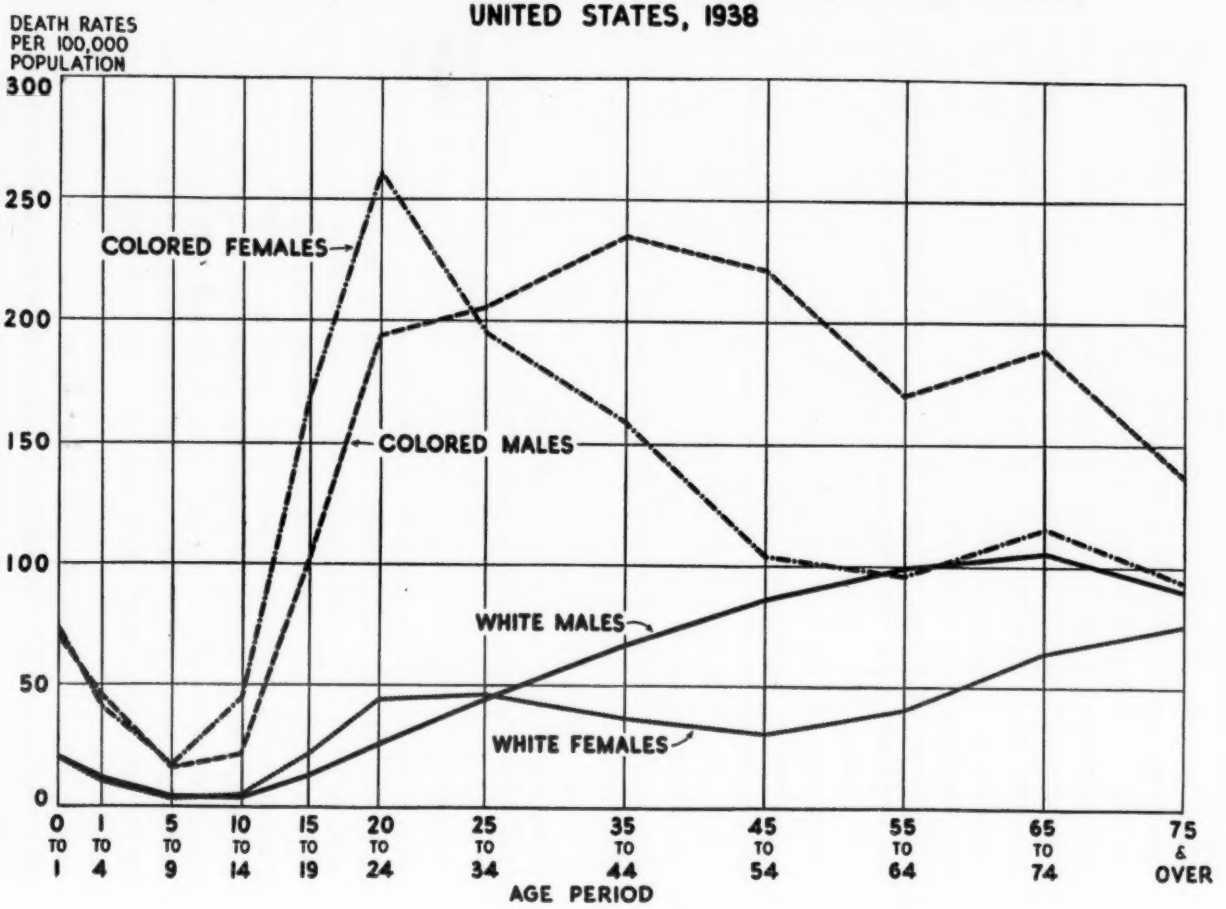

CHART 2

We may then say that tuberculosis in our country is very largely under control among women, except in the childbearing ages; among men, the problem is concentrated at the later working ages of life, up to and including the old ages.

This fact reflects what has been known for a long time, that tuberculosis is very largely associated with the kind of work which men perform. I wish I could present to you an analysis of the current incidence of tuberculosis by occupations. The latest population figures, however, are those prepared by Whitney from data collected in the census of 1930. She showed that certain occupations are heavy contributors to the annual toll of tuberculosis. Recent insurance experience likewise indicates that among workers who are exposed to silica dust, the tuberculosis mortality rate is from six to more than ten times the average for policyholders employed in non-hazardous occupations. This applies particularly to metal miners, stone cutters and chippers of metal, but, many other workers, notably tunnel drillers, sand blasters, sand stone wheel grinders and rock workers in anthracite coal mining are also exposed to large quantities of silica dust and have very high death rates from tuberculosis. In addition, we find that tuberculosis shows very high mortality rates among the large group of unskilled workers irrespective of industry; in other words, among the common laborers who are not exposed to any particular hazard, except that incidental to their low income. They suffer from all of the conditions associated with a low standard of life. Recently, attention has been called to the serious hazard from tuberculosis to workers in sanatoria and in hospitals for the mentally afflicted. In such institutions there is, of course, a concentration of exposure to heavy infection, and the records usually show high morbidity and mortality from this disease among such employees.

I wish it were possible to analyze the facts for the morbidity from tuberculosis as we have attempted to analyze the facts of mortality. I am confident that we would, through such a study, find much revealing material on how the campaign has progressed and where future effort should be concentrated and how long it would take substantially to eradicate the disease. But, unfortunately, the recording of cases has until now been rather desultory and certainly incomplete. So unsatisfactory has case reporting been that health authorities have not thought it worthwhile to analyze their records of cases. No State Health Department pretends to know the total number of cases within its jurisdiction. At the present time, there are less than four recorded cases for each death even in the states where most effort has been expended,

although there is good evidence that if all known cases were recorded, the ratio would be more like eight or nine for each death. Much of the remaining mystery of this disease would disappear if case reporting were taken more seriously by health officers and physicians throughout the state, and if the resultant records were carefully analyzed to show the location of cases, their duration under various types of treatment, their ultimate fate as to recovery or death, the relation of cases to one another in the family and many other items of interest to the student of tuberculosis.

To summarize the few facts which I have given, I would say that the tuberculosis problem in the United States shapes up somewhat as follows: The campaign against the disease, taken by and large, has been eminently successful. There are many localities where the disease is now reduced to the point of a minor cause of death. Even for these, the low figures are still declining and at a good rate. The campaign has, therefore, been thoroughly successful and has more than justified itself. There are, however, some areas and, more especially, some cities where the gains have not been great, and where conditions still present a problem for solution.

As I see it, there is the necessity for concentrating attention and facilities in those counties and cities where the disease has resisted control. In these places, care must be taken to contact the colored population wherever there is a concentration of them. It will be vital, furthermore, to give more and more attention to the conditions prevailing among young women and to discover those who need care. Much more must be done than has heretofore been attempted to safeguard older girls and young women. Much more could be accomplished, for example, if a case-finding campaign by means of X-ray examination could be launched in this sex and age group rather than among school children where cases are rare and far between. Effort will also be rewarded if an attempt is made to discover cases and to give adequate treatment to those in occupations where tuberculosis is known to be rife. Thus, it appears that the problem largely simmers down to the discovery of cases and to providing adequate care and treatment for the cases when discovered. It should be entirely possible, through the various agencies of the state and local health departments and the tuberculosis hospitals, assisted by the medical profession and the local tuberculosis associations, to make a thorough-going search for open cases. These will be found more particularly among the contacts of recent decedents from tuberculosis and current open cases of the disease. These are the centres of

infection and there is every reason to believe that the response to such effort will be as sharp and as immediate as it was in those communities where intensive campaigns have been successfully waged.

I speak with some assurance because it has been demonstrated that tuberculosis can be controlled provided sufficient effort is made to attack it at its vulnerable points. There has been altogether too much hesitation and complacency with respect to tuberculosis as a disease to be conquered. There is good evidence that tuberculosis will not be much more difficult to eradicate than have been other communicable diseases. But we must attack it with the same energy, skill and forethought that we have employed against diphtheria or typhoid fever. There are, after all, the striking examples of Framingham, Massachusetts, of Cattaraugus County, New York and the employees of the Metropolitan Life Insurance Company Home Office. Of these three demonstrations the last is in my judgment the most striking. In this group of about 15,000 employees, many of whom are young women, tuberculosis is well on its way out as a factor in morbidity and mortality. Nor is this a chance occurrence. Everything that was accomplished was the result of concerted and intelligent effort toward an end, to discover cases, to find them in the earliest stages and then to give the patients adequate treatment at Mt. McGregor Sanatorium. Perhaps not the least important aid has been the fact that these employees on discharge from the sanatorium find waiting for them a position to which they are physically and mentally adapted. So far as this group is concerned, there has not been the usual wastage of good recoveries such as prevails generally among other sanatorium graduates, who must go back to their homes usually without jobs in prospect, and with inadequate medical supervision afterward. In most communities, rehabilitation and after care have been the weakest link in the tuberculosis campaign. We in the Metropolitan believe that the added costs involved have been well worthwhile.

In much the same spirit of hopeful accomplishment can every community in the country, every state and every city, approach the problem of controlling its tuberculosis. There is much better ground today than there was twenty years ago for the conviction that we are well on the way toward the substantial eradication of tuberculosis. The disease is obviously on the run and if we would only concentrate our armaments and intensify our efforts, it would be a matter of relatively few years, not over twenty, I believe, before complete success would crown our work. If we may be guided by the extension of the current trend lines of the tuberculosis rate there should be no great difficulty. As shown

CHART 3

TREND OF TUBERCULOSIS MORTALITY

DEATH-REGISTRATION AREA, UNITED STATES

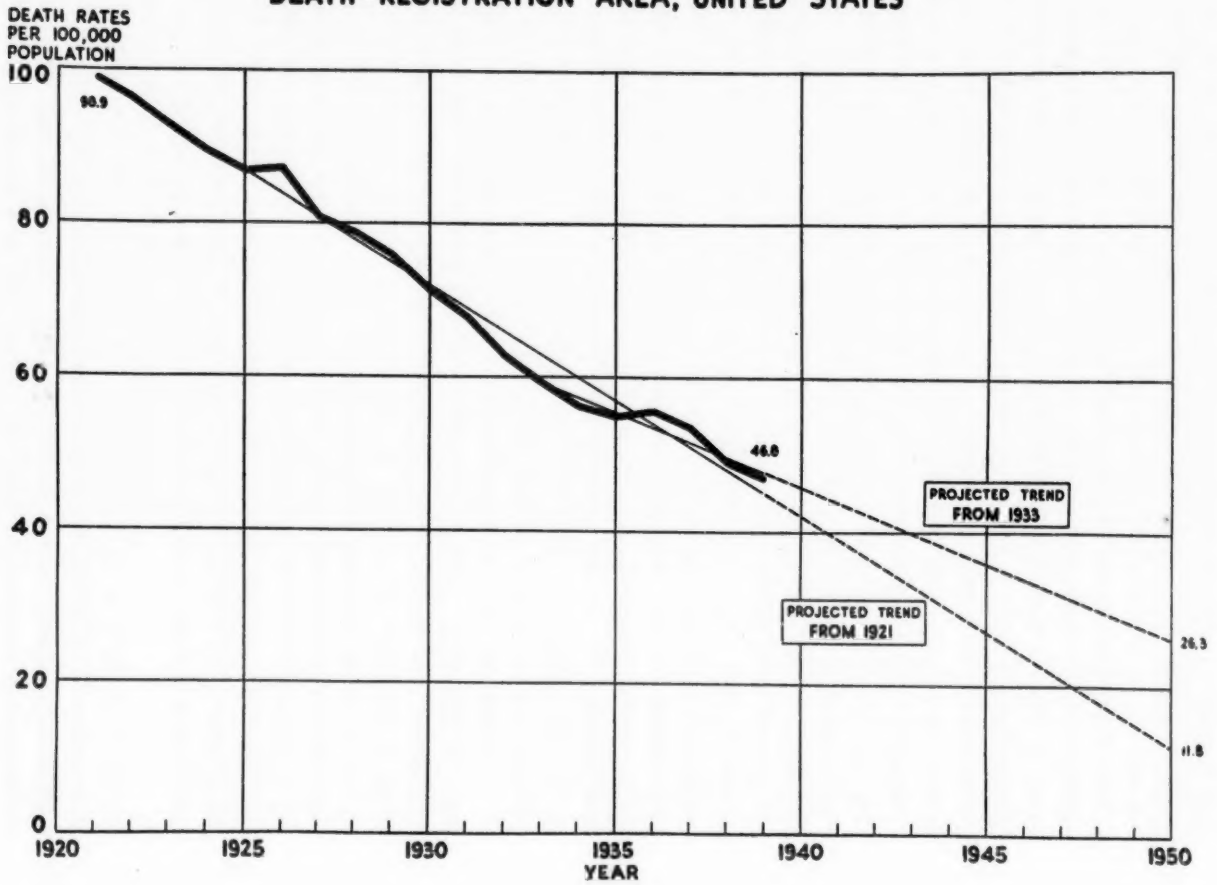

CHART 3

in chart 3, a continuation of the current trends which have prevailed since 1933 should give us a death rate from tuberculosis of only about 26.3 per 100,000 in 1950. But this can be achieved only if our efforts are specifically directed in the areas and on the particular groups where the disease is now most strongly entrenched. It is no longer a job for the shotgun, but for the more selective rifle.

In conclusion, I wish briefly to refer to a line of thought which some of us have had in mind for some time. Remembering Sir Ronald Ross' discussion of the malaria problem some decades ago, we naturally have inquired whether something analogous to his conclusions applied to the problem of the ultimate elimination of tuberculosis from the population. Ross showed that there is a certain *critical* or *threshold* ratio of the infective focus or carrier (mosquitoes) to the human population, which determines whether the disease can maintain itself in the population. Is there some analogous threshold for tuberculosis? Are there now too few open cases or sources of infection to keep the disease going?

Mathematical formulae can be developed which seem to support such a supposition, but practical application of such formulae must for the present remain a prospect only, since many of the data concerning cases are unknown, and even guesses at their number are subject to uncertainties of the order of 50 per cent or more. Without more adequate data especially on open cases, it is evidently impossible to reach conclusions in numerical terms. It is quite likely, however, that for the general population of the country the threshold has actually been passed and tuberculosis is now definitely on the way toward eradication. I hesitate to say when this objective will be reached. Much will depend on how much energy and what new resources are made available in the final mopping-up process. If the plan as recently urged by Homer Folks to the National Tuberculosis Association should be launched in earnest, the time could be much reduced. We must remember also that our population is far from homogeneous or uniform. As I have already pointed out, there are several residual foci of infection among the socio-economically less favored groups, which tend to keep the fires of infection smouldering even after the other strata of the population have reached a position of essential security. It is at these residual foci that a new and enlarged campaign must be primarily directed. The higher economic and social levels have already arrived at a point of relative security from the ravages of tuberculosis. Our aim from now on must be to obtain a similar measure of protection for the lower income levels of our population.

TUBERCULOSIS IN STUDENTS[1, 2, 3]

J. ARTHUR MYERS

Our former conception of tuberculosis was that of a disease, characterized by symptoms and signs such as cough, expectoration, loss of weight, night sweats, hoarseness, pulmonary haemorrhage, râles over the upper half of one or both lungs, X-ray shadows of the same area and tubercle bacilli in the sputum. Any one who had been exposed to the disease and had tubercle bacilli in the body but did not have one or more of these findings was said to be infected but not diseased. Thus, we recognized tuberculosis only after it had entered the consumptive stage. This was the same tuberculosis as the ancient Chinese, Babylonians, Greeks, and all since their time, diagnosed. Ten years ago to say a student had tuberculosis really meant that he had consumption.

In recent years a much more logical conception of tuberculosis has come into being. Those who have adopted it consider that tuberculosis begins when the first neutrophile phagocytoses a tubercle bacillus. This neutrophile may die and promptly be eliminated from the body with the tubercle bacillus it contains and only one human cell has been destroyed. Again, this neutrophile may be lodged in a capillary, where the tubercle bacillus proliferates and the various elements in the defense mechanism appear upon the scene where tubercle is formed. The tubercle bacilli may remain fixed in this position, they may even die; nevertheless, this is tuberculosis. Again, from the initial tubercle, the organisms may be transported by any one of several ways to various other parts of the body. It probably rarely or never happens that a single tubercle bacillus enters the body. Therefore, the original tubercle formation is multiple.

For a period of approximately three to seven weeks after tubercle formation begins, we have no way of detecting the presence of tuberculosis in the body. However, at the end of this period, the tissues are

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sensitized to the protein fraction of the tubercle bacillus and this sensitivity can be determined by the well known tuberculin test. Apparently the tissues remain sensitized to tuberculin as long as tubercle bacilli are alive in the body. Although the tubercles may be microscopical in size, the test betrays their presence. At this point there is no way to determine in a given individual whether clinical tuberculosis will ever make its appearance. Since the body is seeded with tubercle bacilli, clinical lesions may appear at any time and in almost any place. In many persons, after numerous periods of remissions and exacerbations of such lesions, together with the appearance of new ones, the disease destroys organs and may even take life. Therefore, all students who react to tuberculin have tuberculosis. The lesions may be microscopical or gross.

The Tuberculosis Committee of the American Student Health Association, under the splendid directorship of Dr. Charles E. Lyght, reported that 25.5 per cent of 82,774 students examined in the school year 1938–39 reacted to tuberculin. If every test was read correctly, each of these students possesses tuberculous lesions. The same year in 165 institutions with some organized tuberculosis program, 241 students were found to have clinical, progressive tuberculosis and 368, clinical, arrested tuberculosis. Another group of 320 students were back in school after having previously known that they had tuberculosis. Thus, a total of 929 students had developed lesions so large and so situated that they could be located by an examination of the living body. Some were in periods of exacerbation and some in periods of remission at the time they were seen. If one were to cling to the old conception, one might insist that only 929 students in the 165 institutions had tuberculosis in 1938–39 and one might go so far as to state that only the 241 clinical, progressive cases had tuberculosis. Thus, only those that are bordering on or already are in the consumptive stage would be considered tuberculous. However, in every one of these persons the disease began with the ingestion of tubercle bacilli by neutrophiles, and passed through a period of a few weeks before there was sensitivity of the tissues. Even after the sensitivity could have been detected by the tuberculin test, there probably were months or years before any phase of the examination would have revealed the location of lesions. Nevertheless, tuberculosis existed all the time and was gradually but surely passing through its various stages of evolution. The only difference between this group and the larger number who reacted only to tuberculin is that the latter

have not yet developed lesions in the visualized part of the lung large enough to be seen, although such sizeable lesions may be present elsewhere in their bodies.

It is imperative that the modern conception of tuberculosis be accepted not only because it is based upon well established facts but also because it is the only conception that will lead us to the control of the disease. When we see a student who reacts to tuberculin but is not incapacitated in any way, who appears perfectly normal, his X-ray film revealing no shadows or, at most, evidence of calcium deposits, we are not justified in looking lightly upon the condition. We must realize that inspection of the chest by the X-ray does not include all of the lung and that even in the parts inspected there may be lesions still too small to cast shadows that we can see. Moreover, we must not be forgetful of the fact that clinical tuberculous lesions may develop in as many as fifty other parts of the human body and because of the difficulty in examining such parts of the living body, these lesions may remain obscured until they have caused great destruction and marked impairment of the function of the part involved.

The following is a good example. A woman of forty years entered our School of Embalming in November, 1939. She had a record of having reacted to tuberculin on previous occasions. The X-ray film of her chest revealed evidence of calcium deposits in the right hilum region. Otherwise, the lungs appeared clear. However, approximately two years before she had had one ovary, both uterine tubes and the uterus removed because of tuberculosis.

Even if we could be certain that in the tuberculin reactors there are at the moment no lesions except those of the primary complexes, we have no way of determining what minute acute or chronic clinical lesions will develop or where they will be located. The reactor whose complete examination is negative today may have tuberculous meningitis, miliary disease, tuberculous pneumonia, peritonitis, pleurisy with effusion or synovitis, tomorrow. Such a case was previously reported as follows: "Another student entered a university as a freshman in a school of engineering at the age of twenty years on September 27, 1932. He reacted positively to tuberculin, and the X-ray film of his chest made on January 23, 1933, showed no evidence of disease. On May 17, 1937, he was admitted to the hospital. Previous to admission, he had a daily chill for five days. He complained of nonproductive cough, heaviness in the chest and pain between the shoulders. X-ray films of the chest

made on May 18, May 25, June 1 and June 3 were normal. The film on June 25, 1937 showed rather unusual broadening of the superior mediastinum, which suggested the possibility of a mediastinal abscess or tumor. However, the position of the patient was thought to have caused this change. Although the film made on July 17, 1937 was reported as probably normal, death occurred on August 3, 1937. Postmortem examination revealed miliary tuberculosis, involving lungs, liver, spleen, kidneys, thymus, lymph nodes and left seminal vesicle. Miliary tubercles in the lungs ranged from one to four millimeters in diameter and most of them were two to three millimeters and showed evidence of caseation. The hilum and peritracheal lymph nodes and a mediastinal mass were large and caseous."

Another case is that of a girl of twenty-two years who entered our University as a senior in September, 1939. She was a tuberculin reactor and an X-ray film of her chest on November 29, 1939 revealed evidence of a small, sharply outlined density in the base of the right lung, which was thought to represent a Ghon tubercle. On March 2, 1940 she reported because of symptoms which she believed to be due to a cold. They consisted of clearing of her throat, with rather profuse whitish-yellow expectoration. She had only moderate cough. Her temperature was 100.2°F. and she was found to have extensive disease in the left upper lung field, which proved to be tuberculous pneumonia. Tubercle bacilli were abundant in her sputum.

Again, the student who reacts to tuberculin but in whom no lesion can be detected may at any subsequent time have chronic clinical tuberculosis appear in the lungs or in any one or several other parts of the body. For example, in 1930 one of our students reacted to tuberculin but no lesion could be located anywhere in her body. However, in 1935 she had extensive tuberculosis with cavitation in one lung. Tubercle bacilli were present in the sputum. She had cough, expectoration, pulmonary haemorrhage, weight loss and other symptoms of consumption. Such cases with pulmonary lesions as well as those with clinical lesions developing in other parts of the body have not been uncommon in my experience.

Apparently, tuberculosis and syphilis run almost parallel courses; both develop primary lesions. In syphilis the primary attack apparently renders the body immune to exogenous reinfections as long as the spirochetes remain alive in the body; in tuberculosis the primary attack does not guarantee the body against reinfections from exogenous sources.

In syphilis, all spirochetes apparently die in approximately 30 per cent of persons infected even though no treatment is administered, but in approximately 33 per cent, clinical, tertiary lesions subsequently appear in the untreated persons in such places as the central nervous system and the aorta. Obviously, the spirochetes producing these lesions are derived from the primary lesions. In tuberculosis all the tubercle bacilli die in some persons, but we do not know the percentage. However, of those who develop primary lesions it has been estimated that as many as 25 to 50 per cent at some subsequent time have clinical lesions in one or more parts of their bodies. While some of them may be due to reëxposure to persons with contagious tuberculosis, it appears that in the majority the tubercle bacilli are derived from the original primary lesions.

Chronic, clinical tuberculosis is essentially a disease of adults; it increases in frequency with the decades of life. It is only beginning to get into its stride in the college and university age period. Therefore, we must not expect to find more than a small percentage of tuberculin reactors with chronic, clinical tuberculous lesions during their few student years. Nevertheless, enough such cases develop that one must constantly be on the lookout for them. It is of great importance that their disease be detected before it becomes contagious and while many of them can be treated successfully and without causing them much inconvenience. However, the period of three or four years that students are in colleges and universities is extremely significant from the standpoint of conveying to them facts concerning tuberculosis. Those who react to tuberculin should be made thoroughly cognizant of the fact that they may develop clinical tuberculosis while in school or at any subsequent time in their lives; that even the period of senility is not safe from such development. There is no need to alarm them; they have come to the institution to obtain facts on many subjects, and facts concerning health are as important as those concerning any other subject. Having such health facts established in their minds and impressed upon them by an annual examination for tuberculosis should suffice to convince them that such examinations should be made throughout life.

Occasionally one asks why it would not be better to omit the tuberculin test and proceed directly to the X-ray film inspection of the chest, since the occasional person has spoken of this inspection as the best case-finding method. No student of tuberculosis could be satisfied with such a procedure because the X-ray film examination is totally inade-

quate in determining the true tuberculosis situation in any student body. Such examination is limited to a small part of the body; indeed, it does not include more than 75 per cent of the lungs themselves. Moreover, it reveals evidence only of gross lesions and does not differentiate these with reference to aetiology, tuberculous or nontuberculous. We divide pathology into gross and microscopical for teaching and practical purposes. The X-ray reveals only the gross. For example, among those who have primary tuberculosis complexes in the body, the X-ray film of the chest reveals evidence of their presence in only approximately 10 to 15 per cent. The student of tuberculosis demands something far more delicate than the X-ray film and he finds it in the tuberculin test.

It would be as futile to try to control tuberculosis without the tuberculin test as to try to control syphilis without the Wassermann or an equally good test. At the University of Minnesota we have in the neighborhood of 4,500 entering students each year and the tuberculin test indicates that approximately 1,000 of them have the first-infection type of tuberculosis somewhere in their bodies; that is, primary tuberculosis complexes have been established, and to us the tuberculin reaction means that living tubercle bacilli are present. Among our reactors, only 100 to 150 present any evidence that might be interpreted as representing the primary tuberculosis complex on the X-ray film of the chest. Of the entire 1,000, rarely more than 10 or 15 have, at the moment, lesions in the lungs which cast shadows that might be due to the clinical form of pulmonary tuberculosis. Thus, if we depended entirely on the X-ray film examination, we would overlook 85 per cent or more of the students who actually have tuberculous lesions in their bodies. Each of the 1,000 students who reacts to the tuberculin test is a potential clinical case of tuberculosis some time in life and in the occasional one this form of the disease will actually occur while in school. Therefore, we feel that this group of 1,000 students should be listed and observed from year to year for clinical tuberculosis, just as one lists those who have not been immunized against smallpox or diphtheria as the susceptibles in case of an outbreak of one of these diseases on the campus.

Not long ago we attempted to diagnose tuberculosis among students by symptoms, physical signs and the finding of tubercle bacilli in the sputum. These are now recognized as evidences of the later stages of pulmonary tuberculosis. While it is true that the X-ray inspection of the chest often reveals evidence of disease which may prove to be tuberculous before there are symptoms, abnormal physical signs or tubercle

bacilli in the sputum, still, this phase of the examination fails to reveal the vast majority who have small lesions in their lungs and all who have small or gross lesions elsewhere in their bodies. The tuberculin test is not infallible. This has been known for nearly fifty years, yet it excels everything else we have for the detection of the presence of tuberculosis in the human body.

Tuberculosis in cattle runs a parallel course to that in man. Its characteristics are identical in the two species. Indeed, the bovine type of tubercle bacillus is readily transmissible to man and causes much of the primary as well as the clinical tuberculosis in humans, wherever the disease has not been well controlled in cattle. It has been studied in great detail in cattle where various diagnostic procedures, including physical signs, symptoms, X-ray inspection and tubercle bacilli in the secretions and excretions, checked against postmortem examinations which could be made at will. A tremendous volume of this kind of work proved conclusively that the tuberculin test is superior to all other phases of the examination combined. The veterinarians of this country have made more than 217,000,000 tuberculin tests on cattle between 1917 and 1939. The carcasses of more than 3,700,000 reactors were examined postmortem, and the accuracy with which the test selected those with tuberculous lesions was little short of miraculous. Indeed, it was only through the tuberculin test as the detective that tuberculosis has been almost eradicated from the cattle herds of this nation.

The Students' Health Service should determine in so far as possible the exact tuberculosis situation among the students. Administering the tuberculin test and recording the reactions constitutes only a part of an adequate program. Although it detects with an amazing degree of accuracy those who have primary tuberculous complexes, one should determine all other facts possible concerning each reactor. If only a fluoroscopic examination of the chests of the reactors is possible, it should be done. While it is generally believed that this is less accurate in detecting gross lesions than the X-ray film, yet with a special fluoroscopic unit in the hands of one as expert as Stiehm of Wisconsin, it may be equal to the X-ray film inspection. However, most workers still prefer the film because it constitutes an excellent record which can be preserved for subsequent use. The cost of X-ray films in the past has been a serious drawback in tuberculosis work. This, however, has been overcome by the use of the rapid method with paper film, which in the hands of such workers as Lees, of the University of Pennsylvania, is done

at a cost which ten years ago would have seemed impossible. At an extremely low cost, excellent films are produced. Moreover, the method is so rapid that within a few weeks after school begins the X-ray inspection of the chests of all tuberculin reactors can be completed. Although this serves only as a screening process, it is of great value.

No tuberculosis program is complete that stops with the tuberculin test and the X-ray inspection of the chest. Those with shadows of lesions which possibly represent clinical tuberculosis must be examined in considerable detail. Often they are entirely free of symptoms and abnormal physical signs. X-ray film inspection of the chests of such students a month later may reveal that the lesion has entirely disappeared; therefore, it was not due to clinical tuberculosis. In those with shadows that persist, the laboratory plays an extremely important rôle; often there is no sputum to examine, whereupon gastric contents obtained by lavage may reveal the presence of acid-fast bacilli, as has been so well demonstrated by Stiehm and others. Not all acid-fast organisms are tubercle bacilli. Therefore, their pathogenicity must be studied, preferably by guinea pig inoculation. The slow method of introducing these organisms into the body of an animal and waiting six weeks is being rapidly relegated to the discard in favor of much shorter methods which require one-half that time or less.

MUST STUDENTS HAVE TUBERCULOSIS?

With the present state of affairs students in all of our colleges and universities must have tuberculosis; that is, approximately 25 per cent (with variations in different places) who enter as freshmen already have the disease in some form of its development as manifested by the tuberculin reaction. They were infected before they entered college and there is nothing that the institution can do about it. The majority of them are noncontagious at the time they enter and there is no reason whatsoever why they should be refused admission. Nevertheless, they have tuberculous lesions of at least the primary complex and, therefore, one must expect the occasional one to develop evidence of clinical tuberculosis while in school. The only way to solve this problem is to protect all individuals against infection with tubercle bacilli throughout the precollege age. Already this is being done with such success that there is an appreciable decrease in the number of tuberculin reactors among entering students.

MUST STUDENTS CONTRACT TUBERCULOSIS WHILE IN COLLEGE?

The answer to this question is "No", because we have at our command accurate methods of screening out contagious cases of tuberculosis in any group. Therefore, if we keep students under sufficiently close observation, it is with great rarity that one will enter with contagious disease or will develop it on the campus so as to disseminate it to other students. Thus, the students may be prevented from contracting tuberculosis from one another. It is of great importance that no member of the personnel of an institution who has contagious tuberculosis be permitted to have contact either direct or indirect with the students. It is not especially uncommon to find a member of the teaching faculty, a housekeeper in a dormitory, a cook, or anyone else employed about the institution with contagious tuberculosis. In the spring of 1940, one of our students who had become infected while in school maintained that his only exposure was to a faculty member who had tuberculosis. Such cases among personnel of an institution are readily discovered if adequate examinations are required. It is true that the occasional student will become infected through contact with a contagious case entirely apart from the campus. However, in most parts of this country such infections have been reduced to 1 per cent or less per year. Therefore, few students become infected even in this manner while they are in college.

Those institutions which have schools of nursing and medicine have been potent sources of infection for the students. In some such schools, more members of the classes develop the first-infection type of tuberculosis during the brief period they are in college than had developed it throughout all the precollege years. As much as this problem was ignored and as difficult as it seemed to solve a few years ago, there is now a solution in the offing. Indeed, a method is already in effect and while it has not been perfected, it is proving successful. It consists of adequate examination of all members of the personnel of hospitals, as well as all patients who enter. All contagious cases of tuberculosis found are immediately isolated and treated with a contagious disease technique as strict or more so than that employed in other contagious diseases.

During the last fifty years, many attempts have been made to immunize human beings and animals against tuberculosis. Various methods have been employed, such as the administration of tuberculin, so-called immune serum, actual blood transfusions from an animal thought

to be immune, to another that did not have tuberculosis, dead tubercle bacilli and living tubercle bacilli of all the types, both virulent and attenuated. Some of the promoters of certain methods of immunization promised eradication of tuberculosis, but extensive use over the years resulted in failure. There are still a few methods upon which experiments are being performed in various parts of the world, among which is Calmette's vaccine, BCG. This has been in use for more than fifteen years—a sufficiently long time to have been universally accepted—had it been of much value. The medical profession does not lag when a new and efficacious method of prevention or treatment of disease becomes available. For example, insulin, liver extract and toxin-antitoxin were almost immediately accepted and universally used because their efficacy was promptly shown to be beyond question.

Under ideal experimental conditions, the veterinarians of the United States and Canada studied the immunizing qualities of BCG in animals, particularly cattle. It was found of no practical value and was, therefore, discarded. Since more than fifteen years of actual use of BCG in both man and animals has resulted only in controversy, it seems doubtful that it will prove to be of any greater value in controlling tuberculosis than the vaccine von Behring presented in 1901.

Therefore, we must continue to employ weapons against tuberculosis which have been found of universal value. Definitely established facts, when properly applied, are sufficient to control this disease on any campus.

CONSTITUTION AND DIET IN TUBERCULOSIS[1,2]

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The tuberculosis mortality rate has been falling constantly for many years. Recently this decline has been noted for all stages of the disease (1, 2). The various antituberculosis measures have reduced the incidence of infection considerably and likewise have reduced the chances of exogenous reinfection. At the same time those who have clinical tuberculosis have shown a diminishing tendency to die of it. Various reasons are given for this greater survival rate, *viz.*, earlier diagnosis, more thorough treatment, improvement in economic status, lessened hours of work, *etc.* Are these factors alone responsible for the changes which have taken place? There is evidence to suggest that there are other factors that play a part in lowering the death rate. The past twenty years have taught us more certainly that there is an hereditary predisposition underlying many conditions affecting the human body.

Of heredity itself it may be said that inborn characteristics may be transmitted to or continued in the new born generation, be these characteristics normal or abnormal, bodily or mental, structural or functional, important or trivial. These factors may not be recognized always since they remain dormant for want of proper stimuli to make them active.

We know that the make-up or functional habit of the body, known as the constitution, varies considerably even among members of the same family. Until relatively recently, individual constitutions were thought to be solely the product of heredity. In recent years experimental studies have shown that at least some parts of the constitutional make-up can be altered by such means as diet. Whether, in turn, these acquired characteristics subsequently can be inherited remains a matter of dispute. Evolution on the other hand would seem dependent upon such inheritance.

Resistance to disease may depend upon many things, but probably the most important, all other things being equal, is the inherited con-

[1] From the Trudeau Sanatorium, Trudeau, New York.

[2] Presented at a joint session of the Medical and Administrative Sections at the 36th annual meeting of the National Tuberculosis Association, Cleveland, Ohio, June 5, 1940.

stitution. In some infectious diseases, individuals exposed to the infection escape the disease. In local endemics of pneumonia of specific types, the organism has been isolated from the mouths of exposed individuals for a period of months without the individuals becoming ill with the disease (3). Just why this is so has been variously explained. The causative organism supposedly loses its pathogenicity or the exposed individual retains his resistance at a high level. Then, too, it is quite well known that high morbidity and high mortality may be present at the beginning of endemics of disease and that later there may be a low morbidity and mortality. The nonresistant individuals have been weeded out.

What suggestive facts are there which lead to the belief that heredity plays an important part in the course and termination of tuberculosis? From epidemiological studies in tuberculosis, Hill (4) believes that the tubercle bacillus at first weeds out susceptibles in early life when there is no progeny and then postpones the age of fatal disease to and beyond the reproduction age. Susceptibles may then be born again. That such changes have occurred in the past can be seen in the falling death rate from tuberculosis even before the cause of the disease and methods of its prevention were known. Thus Raymond Pearl (5) quotes Pearson as having shown that the tuberculosis death rate in England fell before the general death rate from 1847 to 1866, and from 1866 to 1891 fell more markedly than the general death rate, even though better sanitation was being practiced. Such changes were noted in other countries also.

Groups of people or races previously not exposed to tuberculosis respond to the tubercle bacillus with high mortality from the disease at first and with a declining mortality rate later. Such an occurrence is seen in Ferguson's (6) studies of tuberculosis in the Canadian plains (quoted by Long (7)). Prior to 1880 the general mortality for all causes was about 40 per 1,000. Tuberculosis occurred sporadically only. After these Indians had been transferred to reservations in 1880, tuberculosis seriously increased among them. Soon the disease reached epidemic proportions (1884). In one region, the Qu'appelle Valley, the rate grew to 9,000 per 100,000. Within a decade a great drop in the rate occurred and then a slower drop. Those who in general were resistant to the white man's diseases, survived. Admittedly the change of abode, the disappearance of the buffalo, a valuable food source, the more intimate contact with one another and with the white man and no sound knowledge of sanitation, had a great deal to do with the large

increase in tuberculosis morbidity, but improvement of these conditions does not wholly account for the sudden drop in mortality. A change in the type of lesions also was noted. At first lymph node disease complicating pulmonary tuberculosis was very common. In 1906, 20 per cent of the school children in Qu'appelle were operated upon for tuberculous lymph nodes. Since that time adenitis has rapidly subsided and in 1921 only 7.4 per cent of the school children had lymph node tuberculosis; in 1927 only 2.8 per cent and in 1932 less than 1 per cent. At first the disease was very acute with death occurring within months, but by 1932 the disease had become predominantly chronic, comparable to a similar group of white children. In 1906 the maximum mortality rate was in the age period from birth to five years. Twenty years later the maximum rate was in the ten to fourteen years of age group and from 1927 to 1932 the period of greatest fatality rate was in the age group from fifteen to nineteen years. In other words, the age period of maximum mortality rate among the Indians approached the age period at which the maximum number of deaths occurred among the whites of the same region, *viz.*, twenty-five to twenty-nine years. Other instances of changing mortality rate and acuteness of the disease as the race has been in longer contact with civilization and tuberculosis may be found in the studies of tuberculosis among Eskimos, Negroes, Polynesians, *etc.*

Further evidence of the weeding out of the susceptibles may be found in the changing mortality rate of newly occupied regions as mentioned by Pearl (5). The pioneers usually were of healthy stock and had a low mortality rate from tuberculosis. Later, as the country became settled, less virile stocks arrived. The death rate then rose, reached a peak and subsided.

A study of family histories perhaps leads to a better understanding of the importance of heredity and constitution upon tuberculosis than does a study of the disease in the general population. Geissler (8) reports his studies upon a single couple and their offspring for many generations. The female family was traced to 1746 and the male to 1779. He found a definite lessening of individuals having tuberculosis in the progressive branches of the family tree. The decrease was more than could be accounted for by environmental factors only and was in some measure probably due to the admixture by marriage of nonsusceptible healthy units. Some family groups had unbroken tuberculosis chains from 1805 to 1935, others a recessive incidence. Some families remained free of the disease despite their tuberculous forebears and the

known probability of exposure to massive infection. Geissler calls attention in this respect to the after histories of those unwittingly infected in the Lübeck disaster. Of 251 infants, 71 died in the first year, one in the second year and none in the third. All told, 30.7 per cent died (5 of other diseases). A few of the living later showed calcified mesenteric nodes. Roughly 70 per cent of the infants were resistant.

Raymond Pearl (9) also studied the occurrence of tuberculosis in groups arranged according to the incidence of tuberculosis in the ancestries and found several interesting things, *viz.*: *1:* The proportion of tuberculous offspring increases with the amount of tuberculous ancestry. *2:* The influence of one tuberculous parent is only slightly in excess of the influence of tuberculosis in the grandparental generation. *3:* The influence of a second tuberculous parent doubles that of the first. *4:* The proportion of nontuberculous offspring, although related to, does not vary numerically with the amount of close contact. *5:* The proportion of nontuberculous offspring in contact parentally is high. Struthers (10) quotes Pearl as finding 7 per cent of blood relatives in all generations studied to be tuberculous, whereas only 1.2 per cent of the blood relatives of a nontuberculous person studied were tuberculous. Apparently heredity played an important rôle.

The same probability of inherited susceptibility was found by Turner (11). Another interesting observation by Turner was that the tuberculosis incidence rate was twice as great in bed-sharers as in non-bed-sharers aged fifteen to thirty-five years, but for bed-sharers over thirty-five years of age, who presumably were not of the same parent stock (marriage), this increased rate did not hold true, thus showing the influence of family stock on heredity.

The family records of 4,000 tuberculous individuals in Belfast were examined by Stocks (12). He found that fathers and mothers of tuberculous patients were more likely to have tuberculosis than the parents in the general population and that the children of tuberculous parents were more subject to tuberculosis than the children in the general population. This might be accounted for on the basis of chance of infection, but when the families were divided into groups according to the presence or absence of tuberculosis in the parents and antecedents, he found that the contingency of correlation coëfficients for pairs of children increased with increasing tuberculosis in the antecedents. A result expected on the theory of inheritance but not of infection alone.

Observations by other authors who have made studies of the relation

of racial and family influences to tuberculosis substantiate the probability of an inherited constitution susceptible or resistant to the disease. Among such authors are Goodale (13), Drolet (14), Lee (15), Opie, McPhedran and Putnam (16), Ukil (17), Dickinson (18), Hamburger (19), Macklin (20) and others. One very interesting and recent study is that of Berghaus (21). He studied the problem from the standpoint of extrapulmonary tuberculosis which he thought was specially valuable because of the less frequent occurrence and consequently the more likely to show hereditary influences in sibs (consanguinity). He thought that environmental conditions perhaps did not play such an important part in extrapulmonary as in pulmonary disease. He studied 769 family histories of 16,551 persons, of whom 2,888 had died of tuberculosis. Bone and joint tuberculosis and lupus occurred frequently in some family groups. The site of the lesions was the same in some of these groups, even to the same fingers.

More conclusive evidence perhaps of the inherited factors in relation to resistance to tuberculosis has been obtained through a study of identical and fraternal twins and their reaction to the disease. Such a study has been made by Diehl and Verschuer and reported by Macklin (20). Diehl and Verschuer studied 127 pairs of twins, 45 identical or single-egg and 82 fraternal or double-egg twins. Seven pairs of twins had a common exposure to tuberculosis, but only one of each pair developed the disease. Six of the 7 pairs were fraternal. As 65 per cent of the 127 pairs of twins were fraternal and the fraternal twins formed 85 per cent of the group with tuberculosis, heredity seems to have played a part, as the environment was the same.

Twelve pairs lived in a healthful, identical environment. Five of these pairs had only one member affected. All of these were fraternal. Seven pairs had both members affected. Five of these, or 71 per cent, were identical pairs. Thus with the same environment and differing hereditary response, fraternal twins made up the entire series. With the same environment and the same response, identical twins formed twice as large a group as they should have on the basis of expectation. Both members were affected in 25 per cent of the fraternal twins and 70 per cent of the identical twins. Agreement as to the location and the course of the disease was twice as frequent in identical twins as in the fraternal twins. In fraternal twins disagreement on these points was fourteen times as common as agreement.

In 1938 Uehlinger and Künsch (22) reported Diehl and Verschuer's

80 identical twins with 65 per cent concordance and 125 fraternal twins with 25 per cent concordance. They also reported on 46 pairs of twins studied by them. There were 12 identical pairs and 34 fraternal. In the identical group there was 58.3 per cent concordance and in the fraternal 5.9 per cent concordance. The fraternal twins were composed of 26 of the same sex and 8 of different sex. In the two series of Diehl and Verschuer and of Uehlinger and Künsch, the latter found concordance in the ratio of 1.4 to 1 of discordance in their series, and 2 to 1 in the series of Diehl and Verschuer for the identical twins. Concordance to discordance for the fraternal twins in the Uehlinger-Künsch series was as 1 to 16 and in the Diehl-Verschuer series as 1 to 14. Each series they thought showed the definite influence of heredity.

The influence of heredity in resisting infectious diseases has been shown experimentally in animals. Thus Lewis and White, quoted by Long (7), found wide hereditary variability in the resistance of different stocks of guinea pigs; and Lurie, also quoted by Long, showed that inbred rabbits of varied racial ancestry had, while in cages, low, intermediate and high resistance to inhalation infection with tubercle bacilli. One group contracted tuberculosis soon after exposure and died of generalized disease. Another group contracted the disease only after some time and finally died of a chronic type of tuberculosis. A third group responded in an intermediate manner.

Webster (23) has recently reported a very interesting experiment on the hereditary nature of resistance to disease that has been carried on for fifteen years at the Rockefeller Institute. Selective breeding was used through fifteen generations and individual resistance was a predetermined and known quantity. Highly resistant and highly susceptible mice were bred. Populations were regulated with these strains in varying proportions and a natural infection allowed to spread. It was shown that when only highly resistant mice comprised the population no epidemic of disease resulted. If only susceptible animals formed the population an explosive epidemic resulted which was fatal to nearly all. If resistants and susceptibles were mixed in differing proportions and daily increments of each were added, the severity of the epidemic depended entirely upon the number of the susceptibles. With but few exceptions only the susceptibles became involved. The survivors of an epidemic were almost entirely the known resistants. It appears that the basic inherent resistance of an animal to a given infection is not so much manifest at the portal of entry or in the blood stream as in the

specific tissues to which the agent has a special predilection. Thus, in the "St. Louis" type of encephalitis of mice, the nasal portal of entry of resistants and susceptibles is equally receptive and the blood streams of both contain no antibodies. But in the susceptibles the brain is destroyed and in the resistants only a transitory foothold is obtained and no serious damage results. That the same organs of different species of animals are not affected alike by the same type of tubercle bacillus has been shown by Lange (24), Corper and Lurie (25) and others.

The female constitution at and after puberty differs from the male in many respects. This constitutional difference is reflected in a higher mortality from tuberculosis for girls from twelve to twenty years of age as noted by Putnam (quoted by Opie) in every decade from 1870 to 1920. The same holds true today. This difference in behavior toward tuberculosis is very likely connected with the sex hormones.

Only the hereditary factors of the constitution have been considered so far, but, as stated previously, the constitution can be modified by outside influences not the least of which is the food we eat. Let us consider briefly some of the recent studies and advances made in the knowledge of the relation of food to growth and health. According to Gates (26) plant domestication began probably 10,000 years ago and since then there has been a better selection for food values. This has been more notably true in the past century during which time there have been many changes. The application of Mendel's principles since 1900, especially the study of the structure and division of the chromosomes, has shown how new types were produced in the past by nature and how we can produce them much more rapidly and in an improved form for food purposes. We have learned that not only can the morphology be changed but the chemical composition as well. We have also learned that the chemical composition will be variously modified in quantity by the contents of the soil upon which the food is grown. Thus all potatoes are not the same in quantitative analysis. The same kind of changes have been going on in the animal food world, too. Milk with a greater butter fat content and with larger quantities of vitamins A and D has been produced, so that the relative nutritional value of milk today is greater than in the past. With these changes in food content better nutritional standards have been attained than in the past, particularly is this true for the past twenty years.

Even to-day we know but little regarding the mode of utilization and quantitative needs of the items of nutrition, according to Cathcart

(27). The proper provision of food should be sufficient but not excessive. The effects of insufficiency on the whole are probably less dangerous than the end results of excess. There is a big difference between alimentation and nutrition. The state of nutrition is a clinical state due in part to the provision of food but one to which many other factors contribute very materially, notably the physical and psychical environment. Thus in Australia the Advisory Council on Nutrition found the incidence of malnutrition higher in one group of children six to twelve years of age than in another group of the same age period. The malnutrition could not be correlated with the caloric intake, the total protein, animal protein or the financial income and expenditure of money for food.

Over-alimentation may lead to a state of malnutrition. Maximum growth does not make for health and longevity. Palmer found no relation between height and weight and sickness in 400 children. The ability to grow is retained for a long period of time, though it may be held in check by improper foods only to manifest itself at greater speed when proper food is taken.

Differences in diets do influence the growth and stature of individuals and races. In a study made by Ralli, Connor and Brehm (28) upon the physical state and stature of 240 young male adults compared to that of their parents at the same age period, they found that the present day young male adult is likely to be taller than his father (2.8 inches). It seemed probable that the factors largely responsible were calcium and protein intake. The intake of calcium was about twice that of the fathers and mothers at the same age period and the intake of meat and butter was about 1.5 times that of the parents at the same age period. Rolli states also that Sherman, Osborne and Mendel, Orr and Leighton, and Clark found that the addition of milk to the diet of school children had a markedly greater influence upon growth in height and weight than the addition of an equal number of calories in some other form.

Experimentally in animals Sherman (29) and his associates have been able to control the rate of calcification in the normally developing body by the nutritional intake of calcium in amounts above or below the accepted normal level. This they accomplished without any detectable departure from full health or from the accepted normal physical development. The differences not usually measurable at birth, develop rapidly with early growth, are largest at maximum growth and still significant in adult life. Studies with vitamins A and B show that they increase the length of life. Vitamin A may have the effect of lowering the death rates

in the latter half of the life cycle, that is, the period of adult capacity and vitality has been extended rather than the period of physiological old age.

On this subject Sherman (30) says that the hitherto accepted norms of health and length of life can be advanced, enhanced and improved by a more scientific distribution in the choice and use of food. Previously only heredity had been positively correlated with the length of life, now food and nutrition also are. The chemistry of nutrition is adding its contributions in the prevention of deficiency diseases and the improvement of already normal health and the extension of the life expectation of grown people as well as of children. Protective foods, as classified by McCollum, forestall deficiency conditions and diminish the incidence, the severity and the duration of some diseases other than those primarily nutritional.

Sherman has bred a family of rats whose hereditary and nutritional background has been known for as many generations as would correspond to a human colony where the food supply was known, where the blood was unmixed and where the family tree could be traced in all its branches to a time somewhere between Caesar and Charlemagne. With this rat family it was found that a food supply adequate to support normal growth and reproduction and to maintain health and length of life, might still be capable of much improvement so as to enhance the average nutritional well-being and the higher norms of health at all stages of the life cycle. Growth and development were expedited, higher adult vitality maintained and life expectancy improved corresponding to seven years in the human. The chemistry of human and rat nutrition is strikingly similar in most respects.

Doctor Minot, quoted by Sherman, states that man's future will depend very largely upon what he decides to eat. For two decades the increased consumption of protective foods has been going on and it is very largely because of our use of these foods during the past twenty years that the public health has kept up as well as it has under the stress of the economic depression.

That diet does influence the course of tuberculosis has been well demonstrated by many students of the problem during economic depressions, war, *etc.* One of the latest of such studies is that of Faber (31). During the last World War there was a marked rise in tuberculosis mortality in the belligerent countries as well as in the neutral countries surrounding Germany. In Denmark, where Faber's studies were made,

the rise in tuberculosis mortality did not continue throughout the war as it did in the belligerent countries. The maximum peak in Denmark was reached in 1917, in the war countries in 1918. After 1917 the rate in Denmark fell from 17.6 to 13.8 per 10,000. The rate for pulmonary and extrapulmonary disease fell the same but did not follow the general mortality. The main factor in the rise of the rate was the food shortage. (In Germany in 1916 the food calories per individual reached 1,344 instead of the needed 3,000 daily.) Butter, cattle and bacon were exported from Denmark in great quantities. Margarine largely replaced butter in the diet. There was a loss of vitamins A and D. The consumption of meat and fish fell off. In 1917 the blockade largely prevented exportation of butter. Consumption of this commodity rose from 3.2 kg. per year to 0.25 kg. per week. Consumption of meat rose from 6.2 kg. per individual in 1916 to 29.9 kg. in 1918.

The rise in the tuberculosis mortality in Denmark could not be attributed to housing difficulties since none occurred until after the war and when the decline in mortality had already begun. The food situation appears to have been the major factor. The total calories consumed was not essentially diminished since the supply of bread was ample. But there was a shortage of meat, fish and butter. The incidence of keratomalacia and xerophthalmia was markedly increased from 1915 to 1917 in the poorer families where there was a lack of vitamin-A intake. These conditions had almost disappeared by 1918. However, when the consumption of milk and butter fell again the following year, these two conditions reappeared but the tuberculosis mortality rate continued to decline. The consumption of meat and fish seemed to parallel the mortality curve. The consumption of vegetables did not.

From this study it would seem that the protective foods played an important part in the resistance of the individual to tuberculosis.

While the so-called protective foods do play an important part in the maintenance of good nutrition and resistance to disease, other food constituents must also be borne in mind. Thus, as in all infectious diseases, active tuberculosis makes great demands upon the stored vitamin C of the body. Urine and blood tests show that in this disease there is a decrease in stored vitamin C. The subvitaminosis C roughly parallels the activity of the disease (32). Nevertheless it has not been shown that an excess of vitamin C will inhibit in any way the development of tuberculosis in guinea pigs (33). There does not seem to be any marked

lowering of the vitamin-A content of the body discoverable by the biophotometry test (34). Yet most vitamins are somehow connected with one another in their function and a deficiency in one may interfere with the utilization of another. Thus a deficiency of B1 is accompanied by a decrease in the C content of the organs, the lungs being the first and most markedly affected (35). So for the maintenance of resistance at its highest level adequate supplies of all vitamins are necessary. The general knowledge of this fact and the greater use of vitamins A, C and D have very likely influenced the lowering of the incidence of intestinal tuberculosis (36).

Mineral salts, especially calcium, are necessary for the proper maintenance of health and resistance to disease. These salts, calcium, iron, manganese, iodine, *etc.*, do influence nutrition even though only very small amounts are necessary. Thus manganese seems to have an influence on the utilization of B1 as smaller amounts of B1 are needed for health when manganese is present in the body (37).

And so, through our better knowledge concerning health and nutrition, through the production of better nutritive foods, the greater emphasis on nutritive value rather than on calories, and the popular belief in the necessity of vitamins and minerals, the inherited resistance factor has been enhanced. Better health and nutrition through diet has brought the less resistant to a more resistant state and given them a better chance to survive, once tuberculosis has been established.

SUMMARY

There is much direct and indirect evidence to show that resistance to tuberculosis or susceptibility to it is largely an inherited quality. Such evidence is uncovered by analyses of: *1:* The incidence of the clinical disease and the fatality therefrom in the general population during successive years or periods of the past. *2:* The effect of tuberculosis upon racial stocks. *3:* The effect of tuberculosis on masses of people who have only recently come in intimate contact with it. *4:* The incidence and fatality rates of the disease in family trees or stocks over long periods of time. *5:* The difference in the incidence of tuberculosis between fraternal and identical twins living in the same environment. *6:* The experimental work in animals.

Inherited resistance to tuberculosis can be enhanced or reduced by the food eaten. Evidence of this is obtained from studies on the effect of food shortages on the population during war and other economic

disasters. That nutrition and resistance to disease can be enhanced by the feeding of a larger than usual quantity of qualitative or protective foods, has been shown experimentally.

Isolation of the patient with open tuberculosis has reduced the chances of infection in others and has lessened perhaps the infecting dose and the possibility of repeated infections. Moreover, as the generations have come and gone, natural laws have acted to weed out the susceptibles. Better dietary habits, especially during the past twenty years, have enhanced inborn resistance to all diseases including tuberculosis. These two factors, the inherited constitution and the better understanding of nutrition, have played their part in the reduction of the tuberculosis mortality rate.

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PNEUMOCOCCAL PNEUMONIA COMPLICATING PULMONARY TUBERCULOSIS

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Most observers in the past have considered pneumococcal pneumonia to be rare in patients with active pulmonary tuberculosis. In fact, there has been some question as to whether pulmonary tuberculosis protects the individual from developing nontuberculous pneumonia, more particularly one caused by the pneumococcus.

Pagel (1) reports a case in which he demonstrates how an arrested case of pulmonary tuberculosis may become activated following a pneumococcal pneumonia. Weigert (2) in 1886 was aware of this because he speaks of the flaring up of a tuberculous process after measles as being due to a nonspecific inflammatory process in the lungs, invading the capsule of a caseous lymph node and liberating the tubercle bacilli enclosed within it. Upham (3), in mentioning the complications of pneumonia, states that there is a distinct possibility of tuberculosis developing. He says that the convalescence of all cases of pneumonia must be closely watched for this danger and every measure taken to protect the patient and restore his resistance as promptly as possible. Flick (4) states that pulmonary tuberculosis is preceded by an attack of lobar pneumonia in nearly one-fifth of the cases studied. Austrian (5) and others, however, believe that the acute initial symptoms in such cases are frequently not due to a pneumococcal infection but to an acute tuberculous pneumonic process. Cecil (6) states that in a survey several years ago at the Trudeau Sanatorium there were out of 5,000 patients only 2 proved cases of nontuberculous pneumonia complicating an already existing pulmonary tuberculosis. Brock (7) states that he has seen only one proved case of pneumococcal pneumonia complicating pulmonary tuberculosis at the Waverley Hills Sanatorium during the past thirteen years. He feels, however, that it may be more common than supposed, particularly in terminal cases. Crawford (8) reported one case in 1939 of an unquestionable pneumococcal pneumonia com-

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plicating pulmonary tuberculosis in a twenty-two year old male. This patient had proved tuberculosis for three years prior to the onset of this acute pneumonic infection. He suddenly developed a lower lobe consolidation with all the symptoms and signs of a pneumococcal pneumonia. X-ray revealed consolidation as indicated. This patient was treated with sulfapyradine and had a remarkable recovery and showed no activation of his pulmonary tuberculosis. Brown and Hayes (9) have said: "There is no apparent reason why we should not find pneumococci causing lesions in a person with tuberculosis." These two observers state that pneumococci may be found in the blood stream and in various organs at autopsy in individuals dying of pulmonary tuberculosis.

The following case reports are of two tuberculous patients with complicating pneumococcal pneumonia. Both cases were successfully treated with sulfapyradine.

CASE REPORTS

E. B., white female, aged fifty-four, was admitted to Waverly Hills Sanatorium on October 13, 1939. The chief complaints during the past three years were frequent colds, cough, expectoration, pleurisy, lassitude, blood-streaked sputum and marked loss of weight. In July, 1939 tubercle bacilli were found in the sputum. Physical examination of the chest revealed moderately coarse râles in the upper part of both lungs. X-ray films showed a moderate amount of infiltration and fibrosis extending throughout both lungs. There was a small cavity underlying the right calvicle. Barium meal revealed tuberculous colitis. There were no other complications.

This patient was placed on sanatorium care. Her course was uneventful until January 17, 1940 when she developed an upper respiratory infection with sore throat, nasal congestion and cough. She complained of feeling chilly on January 19, 1940 and her temperature rose to 102°F., pulse 130, respirations 30. On the same day she complained of pain in the right side of her chest on inspiration. Showers of scattered râles were found over the right base. Fluoroscopic examination showed some haziness over the right lower lobe. It was felt at this time that the patient had developed a pleurisy. The temperature on the following day reached a peak of 102.4°F. with the same symptoms persisting. On the 21st the temperature fell almost to normal and she seemed to feel a little better. On the 22nd and 23rd, however, she developed evidence of definite consolidation in the right lower lobe. She became quite dyspnoeic, cyanotic, and her pulse was rapid and thready. She appeared very toxaemic. The sputum became tenacious and had the typical "prune juice" appearance. The temperature during this twenty-four hour period ranged between 100.5°

and 102°F. On the 23rd she had 3,860,000 red cells, 47,300 white cells and 57 per cent haemoglobin. There were 94 per cent polynuclear cells.

An X-ray film on this date showed in addition to the extensive tuberculosis a definite haziness over the lower two-thirds of the right lung indicating early consolidation. Sputum examination showed numerous type-VII pneumococci. Our impression at this time was that the patient had developed a pneumococcal pneumonia complicating her tuberculosis. She was placed in an oxygen tent. On the 23rd she was started on sulfapyridine. Doubt was expressed as to whether the patient would survive. Within the next twenty-four hours, however, the temperature dropped to normal, pulse to 98 and respirations to 30. During the next three days her course was progressively toward improvement. Sulfapyridine was discontinued on the 26th after a total of 270 grains had been given. The temperature remained normal until February 4, since which time she has continued to run a low grade fever in keeping with her tuberculous involvement. An X-ray film taken on February 27 showed a moderate clearing of the pneumonic process in the right base, but there is definitely more involvement in this region than before the complicating pneumonia. The patient has gradually regained her strength and at present feels as well as she did prior to the pneumococcal complication.

J. H., white female, aged sixty-three, was admitted to Waverly Hills Sanatorium in March, 1928 with the chief complaints of loss of weight, lassitude, frequent colds and expectoration which was occasionally blood-streaked. These symptoms dated back to one year prior to admission. X-ray films showed marked fibrosis in the upper third of the left lung and some infiltration and fibrosis in the upper third of the right lung. Tubercle bacilli were not found in her sputum. In view of the history and X-ray findings a diagnosis of moderately advanced pulmonary tuberculosis was made. She was placed on sanatorium care and was discharged on June 15, 1928 as apparently arrested. Since discharge in 1928 the patient states that she has had lassitude, frequent colds, chronic cough and expectoration of one to two ounces of sputum daily. Sputum examinations on several occasions since 1928 have all been negative. She lost fifteen pounds in weight during the four-month period prior to her present illness. On March 9, 1940 she developed an upper respiratory infection with a sore throat and a cough, productive of yellowish-white phlegm. She awakened on March 10 at 4.00 a.m. with a hard shaking chill which was followed by a rise in temperature to 103°F. Cough was persistent and became productive of blood-streaked sputum. Sharp pain developed in the right side of her chest which was exaggerated on inspiration. Dyspnoea developed, symptoms became progressively worse and she was admitted to the Louisville City Hospital. On admission the temperature was 103°F., pulse 120, respirations 25. The skin was hot and moist and there was a catarrhal discharge from the nose. The tongue was coated and furred and the pharynx was

injected. An X-ray film of the chest on admission showed rather marked fibrosis in the upper portion of the left lung and an increased density in the upper lobe of the right lung consistent with a lobar pneumonia. A blood culture taken on the same day was positive for type-I pneumococci and the sputum was also found to contain large numbers of type-I pneumococci. Blood count on admission revealed 3,200,000 red cells, 15,900 white cells with 91 per cent polynuclear cells.

Sulfapyridine was started on March 10. Initial dose of 2 g. was given followed by 1 g. every four hours. The patient became very nauseated and vomited repeatedly. However, within thirty-six hours the temperature had reached normal with a pulse of 82 and respirations of 20. There was also marked clinical improvement otherwise. Due to the excessive nausea the sulfapyridine was discontinued on March 13. At this time the sulfapyridine blood level was 10.6 mg. On March 14 the temperature again rose to 100°F., pulse was 100, and respirations 28. Sulfapyridine was again started with 1 g. every four hours. In spite of this she has continued to run a low grade fever. Blood count taken on the third of March showed 4,560,000 red cells, 8,050 white cells with 75 per cent polynuclear cells. Sulfapyridine was discontinued on March 21. Repeated sputum examinations for tubercle bacilli were negative. Sputum cultures for pneumococci after she began to improve were negative, as was also another blood culture. The patient was transferred to Waverly Hills Sanatorium on April 18, 1940. At the present time the pneumonic area in the right upper lobe has almost completely cleared. The lesion in the left apex, which is her original tuberculous lesion, seems unchanged with evidence of cavitation in this fibrotic area.

The following case report is of a patient who died with pneumococcal pneumonia. No past history of pulmonary tuberculosis was obtained, but the postmortem examination revealed pulmonary tuberculosis in addition to the pneumococcal pneumonia.

D. R., colored male, aged fifty-one, was admitted to the Louisville City Hospital in September, 1938 with a past history of a chronic cough for the past four years. There was an acute onset of the present illness on September 10, 1938 with a chill followed by a rise in temperature. On September 11 his cough became productive of blood-streaked sputum. He developed pain in his left chest and became dyspnoeic on the same day. On admission to the hospital his temperature ranged between 99.6° and 104°F., his respirations were 28 and his pulse was 118. Physical examination of the chest showed a respiratory lag on the left side with an increased tactile and vocal fremitus, impaired percussion note and bronchial breathing from the mid-lung field into the apex on the left side. Coarse râles were heard in the left apex. An X-ray film of the chest on admission showed uniform opacity in the left lung from the first to the fifth interspace. The right lung showed many small shot-

like calcified tubercles. The laboratory findings on the same day were: white cells 9,800, polynuclears 60 per cent, lymphocytes 40 per cent and haemoglobin 12 g. The sputum contained type-III pneumococci, as revealed by culture. A blood culture taken at the time of admission was also positive for type-III pneumococci. The patient became progressively worse and expired about eighteen hours after admission.

Postmortem examination showed dense adhesions over the entire left lung and very firm adhesions over the apex of the right lung. The right lung weighed 780 g. There were multiple calcified tubercles scattered throughout this lung. The left lung weighed 1720 g. The entire lung was consolidated, but the consolidation was more marked in the upper lobe. The cut surface permitted a steady flow of light yellow exudate. Bacteriological studies of this exudate showed type-III pneumococci. There were also scattered calcified tubercles present.

The histological examination of the left lung was consistent with the gross pathological diagnosis of pulmonary tuberculosis and pneumococcal pneumonia. Special staining of tissue sections from the left lung showed tubercle bacilli.

SUMMARY

1. Three cases of pneumococcal pneumonia complicating pulmonary tuberculosis are reported.

2. Two of the cases treated with sulfapyridine recovered from the pneumococcal pneumonia.

3. It is our belief that if a careful postmortem examination is made many tuberculous patients will be found to have a complicating terminal pneumococcal pneumonia.

We wish to express our appreciation to Dr. Benjamin L. Brock, Waverley Hills Sanatorium, and to Dr. A. J. Miller, Pathology Department, Louisville City Hospital, for their kind assistance.

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DEMONSTRATION OF TUBERCLE BACILLI[1]

A Comparative Study of Culture and Guinea Pig Inoculation

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There are two phases in pulmonary tuberculosis where it is of great importance to establish the presence or absence of tubercle bacilli in the material excreted from the bronchial tree. The first is in the confirmation of the clinical diagnosis. Here repeated examinations may be necessary. The second phase is where the retrogression of the disease suggests to the clinician that a point has been reached where tubercle bacilli are no longer being discharged. In this latter phase great care must be exercised to rule out the possibility of a few bacilli being discharged, for tuberculosis often regresses pathologically to a point where clinical and casual laboratory findings become negative.

In the two phases mentioned above tubercle bacilli may be present in very small numbers and intermittently. This necessitates the use of a refined technique to demonstrate their presence. Until fairly recently it had become an established procedure to concentrate the available material and to inoculate the concentrate into guinea pigs. With the development of culture media suitable for growing tubercle bacilli, there have appeared in the literature articles which advocate the use of cultural methods in preference to guinea pig inoculation as much the more economical procedure. As an extensive review of the literature is hardly warranted here, attention is directed to the following articles in the American literature which may be regarded as of greatest significance in recent years relative to a comparison of culture and guinea pig inoculations in detecting tubercle bacilli: Woolsey (1), Herrmann, Hansmann and DeCapis (2), Norton, Thomas and Broom (3), Hirschberger (4), Murphy, Willis, Duerschner and Rhoades (5), Guggenheim and Finkelstein (6), Whitehead (7), and Hoyt, Holzwart, Kuntzner and Fisk (8).

The purpose of this communication is to present the data obtained from a comparative study of culture and guinea pig inoculation of

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specimens for the detection of tubercle bacilli. During the past eighteen months, 1,270 specimens from tuberculous and nontuberculous patients have been examined. These were composed of the following: gastric contents, 627; sputa, 240; urines, 364; pleural fluids, 18; blood, caseous material and miscellaneous, 21.

Pleural and spinal fluids have been concentrated by centrifuging. Bloods have been prepared by haemolyzing with sterile distilled water, followed by concentration in the centrifuge. Gastric contents are treated with an equal volume of 6 per cent sodium hydroxide, shaken and digested for twenty minutes at body temperature. One to four parts by volume of 4 per cent sodium hydroxide are added to sputa, followed by digestion for twenty minutes at body temperature. The specimens are shaken occasionally. For all urine examinations, twenty-four-hour specimens are collected in sterile bottles and placed in the ice box over night. The supernatant urine is decanted and the sediment is concentrated by centrifuging. To the concentrated sediment an equal volume of 6 per cent sodium hydroxide is added and digestion is carried out in the same manner as for sputa. Caseous material and tissues are ground in a sterile mortar and then four parts by volume of 4 per cent sodium hydroxide added. Digestion is carried out as described for sputa. Following these procedures all specimens are concentrated by centrifuging for twenty minutes at 3000 r.p.m. The supernatant fluid is discarded and the sediment carefully neutralized by adding a sterile 1.5 per cent solution of sulphuric acid saturated with phenolphthalein. The neutralized sediment is resuspended in sterile physiological saline solution equal to the original volume. Concentration is again carried out in the centrifuge for twenty minutes at 3000 r.p.m. and the sediment is then ready for testing.

For culturing, two loopfuls of sediment are transferred to a tube of each type of culture medium. The remaining sediment, suspended in 2 cc. of sterile physiological saline solution, is inoculated subcutaneously into the groin of a guinea pig.

A modified Petragnani and a Bordet-Gengou medium have been used in this study. These two types have been employed since the Bordet-Gengou medium is acclaimed to be superior for the growing of the bovine type of tubercle bacillus and the Petragnani for the human type. The formulae for the two types of media are as follows:

MODIFIED PETRAGNANI

A. Fresh milk ..... 600 cc.
Difco peptone ..... 3 g.
Glycerol ..... 48 cc.
Sliced Irish potato ..... 300 g.

This combination is autoclaved at 15 pounds pressure for thirty minutes and is then strained through sterile gauze.

B. Eighteen good-sized fresh eggs are placed in 80 per cent alcohol for two hours. The eggs are then dried by passing through a flame. Fourteen whole eggs and the yolks from the remaining four are thoroughly mixed. They are then filtered through sterile gauze.

C. A one per cent solution of congo red or malachite green in distilled water is sterilized by autoclaving at 15 pounds pressure for thirty minutes.

The medium consists of 400 cc. of A; 600 cc. of B; and 15 cc. of C. After thorough mixing, the medium is distributed to test tubes which have previously been plugged with cotton and sterilized. The tubes of media are then inspissated in a slanted position for one hour at 85° to 90°C. If sterile technique is followed, a second inspissation is generally not required and should be avoided if possible.

MODIFIED BORDET-GENGOU

A. Fresh milk ..... 500 cc.
Glycerol ..... 25 cc.
Sliced Irish potato ..... 200 g.

The mixture is autoclaved at 15 pounds pressure for 30 minutes and is then strained through sterile gauze.

B. Sterile 3 per cent agar.

C. Sterile defibrinated blood.

The medium consists of 300 cc. of A; 700 cc. of B; and 200 cc. of C. A and B are thoroughly mixed and cooled to 60° C. after which the blood is added, and the medium is distributed to previously plugged and sterilized test tubes and allowed to harden in a slanting position. We have used guinea pig and rabbit blood and have found both satisfactory.

The rather complicated methods of digestion and concentration outlined above are very necessary if cultures of tubercle bacilli are to be obtained. Even with the care we have used, a few cultures, as will be shown later, were so badly overgrown with bacteria that they had to be discarded.

The technique outlined above has been in use in our laboratory for several years. To determine the reliability of the method, especially for culturing the tubercle bacillus, we have recently cultured the splenic tissue from tuberculous guinea pigs. Spleens were ground in a sterile mortar, digested and concentrated. From 100 consecutive tuberculous guinea pigs 97 positive, 2 negative and one contaminated cultures were obtained. Macroscopical growth in the tubes was evident in from ten to forty-eight days with an average of twenty days. In this experiment it was quite obvious that the time at which the growth became visible was dependent upon the number of bacilli seeded; the culture with numerous colonies became visible much sooner than those with fewer colonies. From this study it was quite evident that the method of handling the specimens is satisfactory for cultural work.

Our routine procedure of examination of the culture and of the guinea pigs after inoculation was as follows:

All cultures were examined at weekly intervals and the date of macroscopical growth of tubercle bacilli recorded. Cultures were kept for three months before being finally recorded as negative. All of the guinea pigs were tuberculin tested at the end of four weeks. If there was a positive reaction the animals were promptly sacrificed. Otherwise the animals were sacrificed at the end of six weeks. This procedure is standard in our laboratory for all routine tests for the tubercle bacillus. Careful autopsy of each animal was made and if there was any doubt about the infection being tuberculous, smears from lymph nodes or spleen were made and searched for acid-fast bacilli. In case an animal died in less than four weeks after inoculation the test was recorded as unsatisfactory unless there was definite evidence of tuberculosis at autopsy.

In the 1,270 specimens examined, 115 guinea pigs died prematurely and 52 cultures were discarded because of contamination. In 26 instances the guinea pig died prematurely and the culture was contaminated. There were 141 specimens in which either the guinea pig died prematurely or the culture was contaminated. This leaves 1,129 specimens in which a comparison between the results of the guinea pig inoculation and of the culture is possible. In 918 instances both tests were negative and in 211 instances guinea pig or culture or both were positive. A comparison of the culture and the guinea pig as to agreement or disagreement in the positive cases is presented in table 1.

From table 1 it is readily seen that, on the whole, the guinea pig gave

more positive results although there were several instances where the culture was positive while the guinea pig was negative. There were 178 positive guinea pigs and 148 positive cultures. The data here presented will be discussed later.

It is equally important to consider the culture and the guinea pig inoculations in the group of 141 specimens that was deleted from the comparison above. Both of these methods present serious handicaps—contamination of the culture and premature death of the animal. It is

TABLE 1

A comparison as to agreement or disagreement between culture and guinea pig inoculation for the detection of tubercle bacilli

RESULT	TOTAL	AGREE	DISAGREE	
			Guinea Pig	Culture
Positive	211	115	63	33
Percentage				
Positive	100	54.5	29.9	15.6

TABLE 2

Results in 141 specimens where either or both the guinea pig and the culture were unsatisfactory

TOTAL	GUINEA PIG DIED PREMATURELY			CULTURE CONTAMINATED	
	Culture Contaminated	Culture Positive	Culture Negative	Guinea Pig Positive	Guinea Pig Negative
141	26	16	73	9	17
Percentage					
100	18.4	11.3	51.8	6.4	12.1

of interest to determine whether by combining the two methods the handicap of each method may be decreased. Table 2 presents the results of the 141 specimens in which culture and guinea pig could not be compared.

In table 2 it is shown that by a combination of culture and guinea pig 17.7 per cent positive results were salvaged. And in this instance the value of the culture is clearly demonstrated as there were less than half as many cultures contaminated as there were premature deaths in the guinea pigs.

A point that might make the culture preferable to the guinea pig in

routine tests for the presence of tubercle bacilli would be an earlier diagnosis on a routine specimen. In the large majority of specimens we have tested, demonstration of acid-fast bacilli in smears from the concentrate has been negative. This indicates that if tubercle bacilli are present they are in small numbers. If under these circumstances a positive diagnosis by culture is possible sooner than by the guinea pig, a distinct advantage is gained. As a comparison with the appearance of growth in our routine tests we have the series of cultures made from tuberculous guinea pig spleens. In the latter group acid-fast bacilli were easily demonstrated in smears from the concentrate. In table 3 the time of appearance of growth in the culture tubes is given for the routine and for the guinea pig group.

TABLE 3

Time of appearance of growth of tubercle bacilli in culture

WEEKS	GUINEA PIG SPLEENS		ROUTINE SPECIMENS	
	Number	Per cent	Number	Per cent
	97	100	164	100
Less than 2 weeks	19	19.5	0	0
2 to 3 weeks	51	52.5	18	11
3 to 4 weeks	22	23	45	27.4
4 to 5 weeks	1	1	41	25
5 to 6 weeks	1	1	39	24
Over 6 weeks	3	3	21	12.6

In table 3 it will be noted that where bacilli have been seeded in considerable numbers, as in the case of the digested tuberculous guinea pig spleens, 95 per cent of the cultures were diagnosed by the end of a month and only 3 per cent appeared after six weeks, whereas in our routine specimens only 38.4 per cent were positive within one month, and in 12.6 per cent of the cases diagnosis was not possible until after the guinea pig from the same specimen had been sacrificed. From this it is apparent that, where bacilli are few in a specimen, no distinct advantage as to an earlier diagnosis is possible unless the culture is positive prior to a positive tuberculin test in a guinea pig at the end of a month. This is further emphasized by the fact that, in the positive guinea pigs in this series, 75 per cent had a positive tuberculin at the end of one month whereas the remaining 25 per cent had a negative tuberculin which necessitated a delay of two weeks in the diagnosis. In other words, at the end of a

month, a positive tuberculin test was present in the guinea pig twice as frequently as a positive culture and the chief value of the culture at this period in a routine procedure would be for it to be positive at the time a guinea pig gave a negative tuberculin at the end of a month. In our series this has been an infrequent occurrence.

Since two types of culture media have been used in our series, it is of interest to note the frequency with which growth has occurred on these media. There were 164 specimens from which growth of the tubercle bacillus was obtained. In 98 instances growth occurred on both media; growth occurred on the Petragnani medium only in 51 instances and on the Bordet-Gengou medium only in 15. In many cases where only one medium showed growth, the number of colonies was very small, one or two. In such instances it is quite possible that, by chance, the few bacilli present were all seeded on only one of the media. All of the cultures obtained had the characteristics of the human type of bacillus.

It has been one of the points of our investigation to determine whether or not the cultures which were positive in those instances where the guinea pigs proved to be negative, or died prematurely, were pathogenic for guinea pigs. To date, the studies from 25 such cultures are available. The procedure has been to inoculate 1.0 mg. of the culture subcutaneously into the groin of a guinea pig and then to allow the animal to live until it developed an open ulcer at the site of the inoculation or to die. In this series, 22 of the cultures produced progressive tuberculosis in the guinea pig. In 3 instances no tuberculous lesions were found when the animals died or were sacrificed six months or longer after inoculation. All of these cultures were typical for the tubercle bacillus in so far as cultural characteristics and morphology were concerned. It is of particular interest that 3 out of the 25 cultures proved to be nonpathogenic for guinea pigs. In 24 other instances where the culture was positive and the guinea pig was negative, or died prematurely, cultures were not tested for pathogenicity because a positive guinea pig had been obtained in the same case either prior to or after the culture.

DISCUSSION

In laboratory tests it is always advisable to adopt the simplest method that will give a maximum of reliable results. On the other hand, a simpler method should never replace a more complicated one until it has been proved to give as reliable results. It is necessary to compare the more complex with the simpler method in a large number of tests before

any recommendations for changes be made. This has been our objective in a comparison of the somewhat simpler cultural method to the guinea pig inoculation for the detection of tubercle bacilli in suspected material.

The culturing of the tubercle bacillus directly from sputum or other material is by no means a simple matter. The care with which the culture medium must be prepared; the necessity of partially sterilizing the suspension to be cultured in a way to destroy a majority of bacteria that reproduce rapidly and still not destroy the tubercle bacilli; and the advisability of concentrating the specimen, using sterile precautions in the process, demonstrate clearly that to culture tubercle bacilli successfully as a routine procedure involves a decidedly complicated technique. It is one that the average laboratory technician can handle only after careful training and considerable experience.

While a great advance has been attained in the culturing of the tubercle bacillus, it still remains a fact that some strains of tubercle bacilli are extremely difficult to grow. It has been our experience on occasion that, only after repeated attempts, have we been able to obtain a culture of the bacillus from human or animal material. In the data presented above it will be noted that on two occasions out of 100 samples the tubercle bacilli failed to grow although they were present in considerable numbers in the material. Because of this fact one cannot be sure that a negative culture is always correct, although it is reliable in the large majority of instances.

Another fact brought out in our data is that one cannot be sure from the appearance of a culture whether or not it will be pathogenic for the guinea pig. In 3 instances where culturally and morphologically the strains were typical for the tubercle bacillus, inoculation of 1.0 mg. into guinea pigs failed to produce progressive disease. It is now common knowledge that all strains of tubercle bacilli do not have the same degree of pathogenicity. From studies of laboratory cultures it has been possible to obtain strains of high and of very low pathogenicity from a single original culture. It appears that, if a sufficient number of cultures be obtained directly from human sources, a considerable degree of variation in pathogenicity for the guinea pig can be demonstrated. In the 3 instances where our cultures were nonpathogenic for guinea pigs, the specimens had been obtained from cases diagnosed as having clinical tuberculosis. The significance, if any, of such findings remains for the future to determine. Our chief interest in the problem at present is to call attention to the fact that caution should be used in any at-

tempt to label a culture as pathogenic from cultural and morphological appearances only.

In our data the guinea pig gave a significantly greater percentage of positives than did the cultures. This does not necessarily argue against the culture in case one decides to rely entirely on this method. We used but two tubes of culture media whereas Murphy *et al.* used as high as eighteen per specimen. If all of a concentrate were used it is probable that a higher percentage of positive cultures would have been obtained. It can also be argued that, if the entire concentrate were inoculated into guinea pigs, a higher percentage of positives might also have been obtained. If the economy of the test is the desideratum, then the use of a large number of tubes of culture medium for each test would add considerably to the expense, if one considers the material and the labor involved. Considering the problem from all angles, we are of the opinion that the guinea pig is still the test for pathogenicity and that at the present time this is a feature of great importance.

In the series herein reported we have used two types of culture media. Since no cultures of the bovine type have been obtained and since a greater number of cultures were obtained on the Petragnani medium, it seemed advisable to use this medium only. For our procedure on routine specimens we now use two tubes of the modified Petragnani medium for the culturing of the tubercle bacillus, together with guinea pig inoculation.

In the majority of instances where there was a positive culture and a negative guinea pig the number of colonies in the culture was extremely few, one to three. With so few bacilli in a sample it is conceivable that, by chance, the few organisms present might have been introduced either into the culture or into the guinea pig. We have had instances where, with repeated specimens from the same patient, a guinea pig has been negative and a culture positive on one occasion, with the reverse being true on another. Where such a condition exists one can hardly conclude that one method is superior to another for the demonstration of tubercle bacilli.

One may list the advantages and disadvantages of the two methods as follows:

1: The guinea pig inoculation demands less meticulous sterile precautions than the cultural method.

2: Contamination in the cultural method will be high unless very careful sterile precautions are observed.

3: Premature death of guinea pigs, especially during the winter and spring months, may be high if the animals are not properly housed and cared for.
4: The guinea pig is the test for pathogenicity whereas the cultural and morphological appearances may prove deceiving.
5: The cultural method is somewhat more economical provided the number of tubes of media used for each test be less than six.
6: An occasional strain of tubercle bacillus is extremely difficult to grow directly from human or animal material.
7: A few tubercle bacilli of lowered virulency may fail to produce progressive tuberculosis in the guinea pig.

From our study we are of the opinion that the use of both methods is preferable even though it adds somewhat to the cost of the test. By using both methods the disadvantages of each method are somewhat cancelled and one can be assured that the results of the routine tests will reflect more accurately the presence or absence of the tubercle bacilli in the specimens submitted for examination.

It is of interest to note that similar results may be obtained when other types of culture media and different methods for the digestion and concentration of specimens are used. In the report of Hoyt *et al.* the volume of data is quite comparable to our own and the results obtained in a comparison of the cultural and guinea pig methods are very similar. In these two instances the culture media and the methods of digestion and concentration were quite different.

SUMMARY

A comparison of results obtained from culturing and inoculating guinea pigs for the detection of tubercle bacilli in 1,270 specimens from human sources is presented. The results obtained from culturing the spleens from 100 consecutive tuberculous guinea pigs, using the technique briefly outlined in the text, are given. The advantages and disadvantages of each method are discussed. To substitute the cultural method for the guinea pig inoculation procedure seems inadvisable. The utilization of both methods counterbalances certain inherent disadvantages in each. As a routine procedure a combination of the two methods will make possible a more accurate detection of tubercle bacilli present in small numbers than is possible where only one or the other method is used.

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REHABILITATION AND AFTER-CARE OF THE TUBERCULOUS[1, 2]

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By way of introduction to a discussion of the rehabilitation and after-care of the tuberculous, I should like to give a brief report of a study now being completed of a group of patients five years after their discharge from sanatoria. This study, carried on jointly by the National Tuberculosis Association and the Vocational Rehabilitation Division of the U. S. Office of Education, was made possible by the wholehearted coöperation of the sanatorium officials and local workers involved.

It included 6,906 patients discharged alive from 75 sanatoria in 15 states in the year 1933. In making the study as complete a story as possible, each patient was studied as to background, diagnosis, treatment, rehabilitation and after-care. When the 6,906 schedules were completed they were edited and prepared for mechanical tabulation.

The following are some of the findings:

1. Of the 6,906 patients, five years after discharge
   52 per cent were alive
   31 per cent were dead
   17 per cent could not be located

2. On admission to the sanatoria
   9 per cent were under 20 years of age
   42 per cent were between 20 and 29
   32 per cent were between 30 and 45
   16 per cent were over 45
   (Note especially that 51 per cent of all these patients were less than 30 years old.)

3. Of these different age groups, five years after discharge we find that
   54 per cent of those under 20 years of age were alive
   57 per cent of those between 20 and 29 were alive
   50 per cent of those between 30 and 45 were alive

4. With regard to education on admission
   12 per cent had education of six grades or less
   25 per cent had education of seven to nine grades
   21 per cent had education of ten grades or more

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[2] From the Vocational Rehabilitation Division, United States Office of Education, Washington, D. C.

It was discouraging to find that the education of the patient on admission was not recorded in 41 per cent of the cases. The story of educational service to them while in the sanatorium or afterwards was no less discouraging. Only 15 per cent received any kind of educational service, academic or vocational, in the sanatorium; only 4 per cent received vocational rehabilitation service after discharge.

5. As to the length of stay in the sanatorium and its relationship to survival:
45 per cent were in the sanatorium for six months or less
34 per cent of these were dead five years later

23 per cent were in the sanatorium for six months to one year
30 per cent of these were dead five years later

20 per cent were in the sanatorium for one to two years
29 per cent of these were dead

11 per cent were in the sanatorium more than two years
27 per cent of these were dead five years later

From these figures it appears that the longer the stay—if he lives to be discharged—the better chance the patient has of survival. Nearly two-thirds of those who were in the sanatorium for more than three years were alive five years after discharge.

6. The figures on diagnosis on admission, while heavily weighted with far advanced cases, are not as unfavorable as in the past:
14 per cent were minimal, of whom 75 per cent were alive five years after discharge

38 per cent were moderately advanced
60 per cent of these were alive five years after discharge

48 per cent were far advanced—of whom about 33 per cent were found to be still alive

7. With regard to involvement:
80 per cent had bilateral involvement, of whom 48 per cent are still living

20 per cent had unilateral involvement, of whom 68 per cent are still alive
It may be of interest to know that of 1,347 cases of unilateral involvement
60 per cent were of the right lung
40 per cent were of the left lung

8. Unfortunately, in more than one-third of the cases it was not possible to ascertain from the sanatoria records the pathological character of the disease.
However, it was found that of 3,993 cases on whom information on pathological character was available
66 per cent of those classed as productive were still alive
37 per cent of those classed as exudative were still alive
28 per cent of those having cavity were still alive
50 per cent of those classed as mixed were still alive

9. Here is a distinctly hopeful sign:
70 per cent of all cases were discharged with consent of the sanatoria
60 per cent of those discharged with consent were alive five years later
Only 33 per cent of those who left without consent survived the five-year period

This is a great improvement over any previous figures for this item. It reflects great credit on the administration of sanatoria that they and their patients get along so well that 70 per cent of the patients remain until discharged on advice of the physician.

In my opinion this study, incomplete as it is, tells a story of definite progress in the treatment of tuberculosis. Five years hence, when those now in sanatoria are studied, we may expect a tremendous improvement over that shown in this study. I base that prediction on the fact that the tuberculosis specialist has made splendid progress in the development of the techniques of diagnosis and treatment of the disease. Everyone who participated in this study was impressed not only at the array of new techniques but also with the fact that the older, tried and true techniques are being applied with greater care and regularity. Furthermore, diagnostic standards are being more carefully observed.

Despite this great progress in the treatment of the disease, however, the picture of rehabilitation and after-care is distinctly dark. I wish now to turn to a discussion of that subject.

Webster's dictionary gives as one of the definitions of rehabilitation this: "To fit to make one's livelihood again." While this definition is broad enough to cover the subject of my discussion, it requires interpretation. For our purposes here, therefore, I propose that we interpret it as the physical restoration, the maintenance of morale, the occupational adjustment and the social stabilization of a tuberculous person, the general objective being to return him to "the stream of life" from which he has been forced by his misfortune. I should like to take a few moments to explain the different factors involved in such a conception of rehabilitation.

In this job we are dealing with human beings as individuals, not as a mass. Each patient presents a separate and distinct set of problems, problems that must be solved in terms of the whole individual. They cannot be solved separately because the human personality is composed of three elements: the physical, the mental and the emotional. These elements are inseparable, they feed and sustain each other. No man has been able to separate them and have anything worthwhile left. If the one be sick the other two are affected. To treat the one, *all* must be treated.

If we keep this concept of personality and its treatment constantly before us we shall not lose sight of the goal of our particular field of rehabilitation, the ultimate return of a tuberculous person to the stream of life.

Physical restoration, the first factor involved in rehabilitation, means of course returning tuberculous persons to a condition of good health and keeping them in that condition. Keeping them in good health not only implies, it necessitates adequate follow-up and after-care. This fact is proven by the high incidence of reactivation and death of patients who do not have such care. When I consider this incidence I am appalled at the amount of money that apparently is spent futilely in dealing with the tuberculous. The cause of these futile expenditures cannot be attributed to any one group. It is probably the fault of all who are dealing with the problem. The tuberculosis specialists have made tremendous strides in the last few years in developing new techniques of treatment of the physical aspects of the disease. But, organization and personnel for after-care of discharged patients have not kept pace with these developments. Well may we ask how long the people of this country are going to continue to remain blind, deaf and mute to the fact that without adequate after-care the tuberculosis patient returns again and again for further treatment.

I do not know just how much the average cost per patient for a stay in a sanatorium is, but I should guess it to be about $2000.00. The study on which I have just reported shows that five years after discharge 31 per cent of the patients are dead; of these dead 26 per cent had had one readmission and 6 per cent had had two or more. Of the 52 per cent who were living, 19 per cent had had one readmission and 7 per cent had had two or more.

A high percentage of these readmissions might have been averted by proper after-care. Most of them were undeniably due to the facts that facilities were not available for a periodic follow-up of the patients; that many of them were unable to secure work suitable to their condition and took work that was too heavy and the working conditions contributed to reactivation; and that, in far too many instances, the financial condition of the patient was such that he could not provide himself with adequate food and shelter. In other words they had not had all the services they needed to rehabilitate themselves.

As a contrast to the figures just given on cases discharged in 1933, I should like to give you figures on 400 cases that were rehabilitated in the

fiscal year 1935–36. Of these 400 cases, reviewed four years after rehabilitation, only 3 per cent were dead, and only 9 per cent had reactivated, as compared with 31 per cent dead and 26 per cent of the living cases, reactivated among those discharged in 1933. Although many of the 400 cases were not given what may be called adequate after-care, it must be admitted that such service as was given in the way of vocational adjustment and follow-up gave them a much greater chance of survival.

The second factor in the rehabilitation of a tuberculous person is the maintenance of morale. I know of no human situation in which the statement that "an idle brain is the devil's workshop" applies so aptly. The mind and the emotions feed upon the materials they find at hand. If they have no better material to feed upon than that supplied by the four walls of a hospital room they have a way of feeding upon each other. Like the gingham dog and the calico cat, they tend to consume each other until the morale of the patient is destroyed and in many cases physical recovery is retarded. Morale is half the game in the rehabilitation of tuberculous persons. Morale is sustained when they have hope of returning to the stream of life. To give them hope there needs to be provided for them during their stay in the sanatorium a service of counsel and advice, not only as to their physical rehabilitation, but as to their emotional adjustment, their occupational future and as to what they can do to improve themselves. They need something tangible on which they can set their mental and emotional teeth, something to give them tangible reason for hope. To this end the modern sanatorium provides social service, occupational therapy, prevocational training and, in a few instances, vocational counselors. Then, when the patient is discharged, he is turned over to the State Vocational Rehabilitation Service for completion of training and placement. Furthermore, the patient is provided with the opportunity of periodic check-up on his physical condition. This kind of a set-up gives the patient reason to hope—and fortunate is he who has such an opportunity.

In his immortal poem, L'Inferno, Dante places over the gates of hell this legend, "Abandon all hope, ye who enter here." If there be tuberculosis sanatoria in this country over the gates of which that legend might properly be placed, let us all here hope that their number is small, and that the reasons why the legend applies are those of finance rather than of attitudes on the part of those responsible for their operation.

The third factor involved in the complete rehabilitation of a tuberculous person is that of occupational adjustment after leaving the sana-

torium. I should like to say at once, that the group I represent, the Vocational Rehabilitation group, has not done all that it might have done in taking care of this factor. The mortality rate has had them frightened. But as more and more of the organizations having the responsibility of dealing with this problem institute modern methods and provide them with more reliable diagnostic and therapeutic work and more information on discharge and provide better after-care, the rehabilitation group is taking courage to increase its services to the tuberculous.

All of us recognize the fact that occupational adjustment is clearly the job of the respective State Rehabilitation Services. They were established for the purpose of serving all physically disabled persons. The tuberculous represent one of the largest disability groups and it is up to all of us to insist that they get due consideration. I should like to point out, however, that what a rehabilitation agent can do for a given patient depends to a large extent upon what has happened to him before he gets to the agent, and on the character of the information the sanatorium is able to provide on what happened.

No one knows a great deal about the occupational adjustment of the tuberculous. It is only through research that we shall be able to develop suitable techniques. The information called for on the medical report form and other information contained in the rehabilitation case folder will provide the basis for research.

As I view it, vocational rehabilitation following arrest of the disease, plus a reasonable amount of follow-up and after-care represent the crux of the problem from an economic standpoint. Treatment of the disease without follow-through to complete rehabilitation, while it may have high sentimental value, has proved to be economically unsound. The vocational rehabilitation of physically disabled persons requires a high degree of coöperative effort on the part of the individuals and agencies involved. This is particularly true of the tuberculous where the physical, emotional and economic situations of the patient loom so large. The rehabilitation agent must of necessity act in the capacity of coördinator and engineer, bringing the coöperative effort of all concerned to bear upon the occupational adjustment of the individual patient. He cannot make a move without the coöperation of the sanatorium superintendent and the physician. To you here who are concerned I bespeak your wholehearted coöperation with the rehabilitation agent in dealing with your patients.

The last factor in the rehabilitation of the tuberculous is that of social

stabilization. By social stabilization we mean the readjustment of the patient to the environment from which he comes or to a changed environment, if the one from which he comes is unsatisfactory. This, of course, is a part of the function of follow-up and after-care. It has been found that many patients reactivate because they have returned to unfavorable home and community environments. Many of them return to homes with inadequate diet, sleeping arrangements and other facilities for the physical care of the patient, conditions which, if they do not contain danger of reinfection, are certainly not conducive to good health. Many of these homes are located in communities where suitable work cannot be obtained, or where there are irritating noises, confusion and other unfavorable surroundings. Under such conditions attempts at vocational rehabilitation and after-care are futile, because any results obtained may at anytime be vitiated by the surroundings. Hence, it is frequently advisable through social service to establish the patient in a new environment. This brings up the matter of boarding homes as a vehicle of transition, a bridge, between the sanatorium and the new environment, and as a safe place in which certain other discharged patients may live during their period of vocational preparation and placement. I hope to see such homes established in every community in which there is need for such an institution.

To summarize this brief discussion; I have implied what I consider to be the essentials of a reasonably adequate provision for the rehabilitation and after-care of the tuberculous. Such provisions would include:

1. Treatment in the sanatorium must include not only treatment of the physical aspects of the disease but also the treatment of the mental and emotional aspects by providing counsel and advice, educational opportunity and prevocational training, the purpose being to give the patient reason to hope, and at the same time an opportunity to improve his chances of occupational adjustment after discharge.

2. Provision for periodic physical check-up after discharge must be provided.

3. Occupational adjustment should be attempted as early as is feasible after discharge.

4. Follow-up service before, during and after occupational adjustment should insure the social stabilization of the discharged patient; a boarding home should be provided wherever the number of patients discharged in a community makes such provision advisable.

In conclusion, the essential factor in carrying out such a program is

organization. The rehabilitation and after-care of the tuberculous cannot be made entirely successful until all individuals and agencies dealing with them in a community get together, organize and promote a composite program and secure financial support for it. In some communities the local tuberculosis association has done this. In many it has not been done. To these latter, I offer the Biblical injunction, "Go and do thou likewise."

EDITORIAL

Clinical Incipiency of Tuberculosis

During the last two or three decades early diagnosis of tuberculosis has had an ever changing meaning and the change, based on rational concepts and aided by methodological improvement, has always been in the same direction: the earlier and earlier recognition of the disease. Unnoticed almost, this change necessitated a readjustment in the terminology of "disease" itself. Early diagnosis is passed when the patient is conscious of "dis-ease." Truly early diagnosis is realized only when it is made in the presymptomatic stage. Whatever definition of disease one may choose, impaired function is almost invariably one factor in distinguishing between the physiological and the pathological. But certainly, tuberculosis in its earliest clinical manifestations has outgrown such terminological restrictions. Completely asymptomatic infiltrations, causing no demonstrable impaired function, are recognized as early disease. It has, then, become necessary to define anew the point of onset of clinical disease.

Dr. J. A. Myers, in a paper in this issue and in a number of previous papers and addresses, proposes that the real onset of the disease is the moment "when the first neutrophile phagocytoses a tubercle bacillus." Considering tuberculosis in all its protean manifestations as a biological entity, Doctor Myers' statement is unquestionably correct, just as correct as the statement that the first evidences of senility begin long before the third decade of life is completed. As the comparison indicates one may wish, particularly in practical application, to scrutinize a statement not only as to its scientific accuracy but as to its pragmatic value, as well.

In support of the view that tuberculosis begins with that first encounter of tubercle bacillus and phagocyte, Doctor Myers quotes the example of a student with normal physical findings but a positive tuberculin test who, three and a half years later, developed miliary tuberculosis. Does not the same thing happen, and possibly more frequently, in youngsters who, three or four years previously, did not react to tuberculin? In other words, can the knowledge of a positive tuberculin test help in foretelling or in forestalling the unfortunate outcome?

Doctor Myers says: "Again, the student who reacts to tuberculin but in whom no lesion can be detected may at any subsequent time have chronic clinical tuberculosis. . . ." But, is not exactly the same statement true for the student who does not react to tuberculin? Are there, then, justification and advantage in the advice that "those who react to tuberculin should be made thoroughly cognizant of the fact that they may develop clinical tuberculosis?" Since undoubtedly a large percentage of primary infections occur after college-age, why should the non-reactors not be equally warned?

It must require a well-nigh magical gift of persuasion to inform a student of the dire potentiality of his outlook, and to convince him at the same time that there is "no need for alarm."

It seems possible that the warning-without-alarm attitude is largely conditioned by the former truth which is no truth anymore in the U. S. A. —that the vast majority of primary infections occurred in childhood. This would—in part, at least—explain the differentiation, at college-age, between the potentially doomed reactors and the ones that live not under the shadow of tuberculosis. But primary infection is not any more synonymous with childhood infection.

How real, then, is the potential danger that the tuberculin reactor faces? Doctor Myers states "that as many as 25 to 50 per cent" of reactors "at some subsequent time have clinical lesions. . . ." What is the basis for this estimate? At the present time about 5 per cent of all deaths are due to tuberculosis. It is probably a generous estimate to assume that only 50 per cent of all patients with clinically significant tuberculosis die eventually of their disease. In this case, 10 per cent of all people in the U. S. A. have, at some time or other, clinical tuberculosis, and since 50 per cent of the population are estimated to be reactors, about 20 per cent of tuberculin reactors would fall prey to clinically demonstrable disease. However, there is a significant mistake in basing the calculation on 50 per cent reactors. These 50 per cent have been estimated on the basis of the living population with the age distribution of this living population. The age distribution at death is shifted considerably to higher ages, as compared to that of the living population; from this it follows that the population at death contains considerably more than 50 per cent reactors, and, hence, the chances of reactors to develop clinical tuberculosis are considerably less than 20 per cent.

It is the obvious to assert that only tuberculin reactors develop clinical disease and may die of it, but this information remains sterile in practical

use, unless it could be complemented by the knowledge of how late in life—if at any time—primary infections do not develop any more; only with such knowledge would it be possible to distinguish, at some time, those in danger and those who are safe.

Does tuberculin allergy spell only doom and danger? All well substantiated experimental work goes to prove that there is only one method by which the resistance against tuberculosis can be raised and that is by infection with tubercle bacilli, living or dead. It is inconceivable that the human animal should be the sole exception, and there are a good many observations, notably those by Heimbeck, that confirm for man the deduction from experimental studies. More cases of miliary tuberculosis occur within the first six to twelve months following the primary infection than at any subsequent period of the infection. The reactor who is well has successfully passed through this critical period.

One more practical point of view remains to be mentioned. If Doctor Myers' concept were widely accepted, life insurance companies would logically refuse to insure reactors or accept them only as substandard risks, civil service would discriminate against reactors, the armed forces would have to reject them.

It seems, then, that it would be wise to speak of tuberculosis as disease or as potential danger only when substantial reasons are demonstrable, and only when action to allay such danger is indicated and possible. Periodic health examinations? Yes. But who can say to-day whether the young person with or without reaction is more in need of them?

MAX PINNER

BRIEF REPORTS

RED HAIR AND TUBERCULOSIS[1, 2]

EMIL BOGEN

Among the numerous characteristics which have been suggested by various writers as evidences of constitutional susceptibility to tuberculosis, may be noted the factor of pigmentation. More than two thousand years ago Hippocrates included in his characterization of the "form of the body peculiarly subject to phthisical complaints" the whitish, the reddish and the blue-eyed. The otherwise quite different scrofulous diathesis of Hufeland was also described as possessing light colored hair and blue eyes. Recent writers on constitution, in Germany, have reversed this notion and suggest that it is the dark complexioned individuals who are more susceptible. Most American workers fail to recognize any definite relationship of pigmentation to susceptibility to tuberculosis, and even such enthusiastic workers as Draper tend to stress shape rather than color in characterizing the tuberculous type. At a meeting of the Los Angeles Trudeau Society, in 1935, Dr. Charles Coghlan maintained that red hair in itself indicated a low resistance to tuberculosis and asserted that red-headed patients rarely recovered.

In the course of a WPA Research Project at Olive View, it became possible to put this claim to objective test. The color of the hair and eyes is recorded by the Admitting Room clerk at the time of admission of every patient to the Olive View Sanatorium as an additional point of identification. Such records are available, therefore, for nearly 10,000 patients admitted during the past two decades. The description of color so given is rather casual and perhaps faulty, depending somewhat on the keenness, perspective and discrimination of the various Admitting Room clerks employed during this time. More than a dozen different terms have been used to describe hair color on these records, including black, dark-brown and brunette, brown, light brown, auburn, blonde, sandy, golden, fair, taupe, gray, white, silver and red. Where several colors have been reported on the same patient in this study, the darker color has been considered characteristic. Although differences of opinion

[1] From the Olive View Sanatorium, Olive View, California.

[2] With the aid of Works Progress Administration, Project Number 665-07-3-223, Los Angeles County, Los Angeles, California.

might exist as to the color of the hair of some of the patients described in this series, it is not believed that many of those called red would be otherwise characterized by various workers.

In view of the difference of opinion as to the description of the brown hairs that constituted the majority of our patients, an intensive examination of the different shades reported has not been undertaken. It was felt, however, that the appearance of red hair was sufficiently distinctive to make such an examination valid. Red hair constitutes a conspicuous and unusual variant

TABLE 1

Red hair and mortality

All red-haired patients, 1920–1937, inclusive

STAGE	TOTAL	DIED	YEARS FOLLOWED	AVERAGE ANNUAL CASE FATALITY RATE
Minimal	15	0	78	0
Moderate	9	2	38	5
Far-advanced	100	56	270	21
Childhood and nonpulmonary	20	2	80	2
Total	144	60	466	12.8

TABLE 2

The mortality experience of the Olive View Sanatorium

All admissions, 1920–1937, inclusive

STAGE	TOTAL	DIED	YEARS FOLLOWED	AVERAGE ANNUAL CASE FATALITY RATE
Minimal	830	60	4,619	1.3
Moderate	1,209	209	4,641	4.5
Far-advanced	5,754	3,237	14,969	21.6
Childhood and nonpulmonary	966	70	4,211	1.7
Total	8,759	3,576	28,440	12.6

representing about 1 per cent of the total number of patients recorded. A study of 144 patients recorded as having red hair was therefore made to cast light on this question.

The red-haired patients admitted to the Olive View Sanatorium were, for the most part, far-advanced cases of pulmonary tuberculosis, over two-thirds being in this category at the time of admission, and over 40 per cent of them were reported as having died by July 1, 1937, figures substantially the same as those for the total number of patients treated during this time.

The average annual fatality rate in this group was 12.8 per cent, a figure

similar to that for the entire group. The fatality rates, by stage, were: minimal, zero, moderately advanced, 5, and far-advanced, 21 per cent, giving an average of 8.6 per cent for a population of equal numbers in the three stages, again similar to that for the entire population.

Individual case records among red-haired patients often revealed striking evidences of resistance to the infection and of the effectiveness of collapse measures in its control, as in one young man with extensive bilateral cavitation, in whom prolonged alternating bilateral pneumothorax and a permanent phrenic paralysis were followed by a complete arrest of the disease. A series of 144 red-haired patients out of a total of nearly 10,000 admissions may be too small for absolute elimination of a remote possibility that some difference in reaction to tuberculosis might be present, but it appears sufficient to demonstrate that such hypothetical susceptibility can have no practical importance in the course of the disease.

TUBERCULOSIS IN MEDICAL STUDENTS[1]

A Survey of 298 Medical Students

ALICE E. BAKER AND JOE E. HOLOUBEK

The relatively high incidence of tuberculosis among medical students has been recognized for many years, but only during the last decade have medical schools undertaken surveys for the detection of tuberculous infection in an attempt at its control (1, 2, 3, 4, 5, 6). Comparatively few studies of tuberculous infection among students of southern medical colleges have been reported. Long and Siebert (7) report Blackford's one-year survey at Emory University Medical School, and Keller and Kampmeier (5) report a six-year survey at Vanderbilt University School of Medicine.

In the short history of the Medical School of Louisiana State University, tuberculosis has taken an unfortunate toll. In the past two years, 5 cases of tuberculosis have been diagnosed clinically among the student body. This survey was undertaken to detect any unrecognized cases of tuberculosis, to formulate a basis for further tuberculosis survey, and to compare the incidence of the infection here with that in other medical schools.

Participation in the survey was not mandatory and 298 students, or 85 per cent of the student body, volunteered to take part. Inasmuch as routine physical examinations at the time of registration had just been completed and had failed to show any evidence of tuberculous infection, these examinations were not repeated. The students were given the routine first and second intracutaneous tuberculin tests with PPD. An anteroposterior chest roentgenogram was made on every student in the survey whether his tuberculin test was positive or negative.

The following criteria were used when interpreting the chest roentgenograms. "No evidence of tuberculosis" presupposes a roentgenogram showing no evidence of calcification in the lungs or in the thoracic lymphatics and no evidence of a parenchymal lesion; "evidence of healed first-infection tuberculosis," a roentgenogram showing only calcification; "evidence of active second-infection tuberculosis," was a roentgenogram showing a definite parenchymal lesion.

RESULTS

(*1*) *Incidence of tuberculin reactions:* There were 259 students (83 per cent) who reacted to tuberculin. The incidence of reactors was slightly higher

[1] From the Department of Medicine of the School of Medicine of Louisiana State University, New Orleans, Louisiana.

among the students from southern homes than those from elsewhere. No correlation could be found between a history of previous exposure and the incidence of reactors.

(*2*) *Tuberculin reaction correlated with numerical value of class year:* Of unusual interest was the increase of reactors according to the numerical value of the class year. Thus 68 per cent (*61*) of the first year students, 90 per cent (*84*) of the second, 94 per cent (*65*) of the third and 98 per cent (*49*) of the fourth year students were reactors.

(*3*) *Tuberculin reaction correlated with chest roentgenographic findings:* Of the 39 students having negative tuberculin tests, 32 students, or 82 per cent, had normal roentgenograms, whereas the remainder showed evidence of calcification (table 1).

Of the 259 students having positive tuberculin reactions, the roentgenograms of 71 per cent (184 students) were classified as showing evidence of healed first-infection tuberculosis, while 2 per cent (6 students) showed suggestive,

TABLE 1

Correlation of chest roentgenographic findings to tuberculin reactions

REACTIONS TO PPD	TOTAL		NEGATIVE		ROENTGENOGRAPHIC FINDINGS					
					Calcifications		Suggestive lesions		Definite lesions	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Positive	259	83	66	26	184	71	6	2	3	1
Negative	39	17	32	82	7	18	0	0	0	0

and 1 per cent (3 students) showed definite parenchymal lesions. The remainder were normal. The roentgenograms showing suggestive and definite parenchymal lesions were associated with positive tuberculin reactions, indicating a group of 9 students with possibly active lesions. Of this group, 3 students have been found to have definitely active lesions. The remaining 6 require further careful study.

(*4*) *Incidence of tuberculin reactors at Louisiana State University School of Medicine compared with that of other medical schools:* The incidence of tuberculin reactors at this medical school is higher than in the two other southern medical schools reported (5, 6), and rates among medical schools reporting the highest incidence.

DISCUSSION

Ours, as well as other surveys (1, 2, 3, 4, 5, 6), indicates the marked increase of incidence of reactors occurring throughout the matriculation-graduation period. In our survey the greatest portion of this increase appeared between the freshman and sophomore year. Other reports display a strikingly similar

phenomenon (1, 2). Inasmuch as the preclinical (first and second year) students of Louisiana State University School of Medicine have no hospital contact with tuberculous patients, these findings would tend to minimize the importance of such contacts in producing positive reactions. Such observations would tend to relate the increase in reactors to a change of environment encountered on entering medical school. Analysis of the part played by environmental factors, such as density of population, the possibility of relatively poorer living quarters, the chance of a low vitamin or (and) a contaminated diet, longer hours of study, *etc.*, was not made in this survey.

CONCLUSIONS

In deciding upon a general method for tuberculosis surveys in a small school with an incidence of 83 per cent positive reactors, one must compare (*1*) the more laborious plan of routine tuberculin testing and X-raying only reactors, (*2*) the cost of tuberculin tests, (*3*) the discomfort experienced by the occasional severe reaction and (*4*) the extremely rare possibility of overlooking a far advanced case, with the more simple procedure of X-raying all students yearly, thus saving considerable time which probably more than compensates for the cost of a somewhat greater number of roentgenograms.

We are indebted to Parke-Davis and Company for the PPD used in this study.

Thanks are given to Dr. Fortier and Dr. Gately and the Hotel Dieu Department of Radiology for making it possible to obtain roentgenograms at a very reasonable cost.

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INTENTIONAL OBLITERATION OF PLEURAL SPACE BY THE USE OF BLOOD[1]

EDWARD KUPKA AND WILLIAM WAGNER

In preparation for draining a nontuberculous lung abscess or for lobectomy, it is necessary to make sure of at least partial obliteration of the pleural space. The purpose of such obliteration is the prevention of collapse of the unoperated part of the lungs during operative procedures and, also, the prevention of empyema.

Frequently the disease process itself has brought about pleural fusion, as in lung abscesses, but when a pneumothorax or potential pneumothorax is present, several methods of obliteration have been suggested in the past, most of them surgical (1). In 1935 Bethune exhaustively listed these methods, stating that he preferred the intrapleural insufflation of talc for the purpose. Among the most popular methods in use today are direct traumatism to the facing pleural surfaces by rubbing with gauze and the packing of gauze tampons against the exposed parietal pleura.

The Monaldi method of cavity aspiration (2, 3) consists of long continued suction in a tuberculous cavity. This end is obtained by transparietal puncture with a trocar-cannula until the cavity is reached and introduction of a catheter through the cannula. The catheter is left in place for weeks or months and through it the suction is applied (4, 5).

Many cases in which cavity aspiration seems indicated have already developed pleural fusion because of the disease. Some have had an inefficient pneumothorax which, when abandoned, did not terminate in complete pleural obliteration. Others, in whom pneumothorax was not attainable, are obliterated throughout most of the pleural surface, but have nevertheless a potential pocket directly in the path of the projected puncture. In the last two groups, steps must be taken to bring about firm adherence of the pleural surfaces in the region of the puncture. If this is not done, the patient faces the possibility of serious complications, such as spontaneous pneumothorax or empyema.

Bethune reported that many substances have been injected into laboratory animals with the object of producing adhesions by the closed method. Most of these either brought about no adherence at all or caused a very violent reaction with necrosis and abscess formation. Some caused a few thin tenuous

[1] From the Olive View Sanatorium, Olive View, California.

adhesions which readily separated. Among these substances he named tincture of iodine, ether, alcohol, formaldehyde, gomenol, silver nitrate, sudan-III, glycerine, gum arabic, turpentine and dextrose solutions.

The patient's own blood may be used as the obliterating substance. The use of blood for pleural obliteration was first suggested by Dr. Jose Argemi Lloveras of Barcelona, Spain, one time Fellow at the Forlanini Institute. It has been observed that whole blood in the pleural space, if not quickly and completely withdrawn, will cause thickening of the pleura and usually obliteration of the pleural space. Maxwell (6) repeats this point about intrapleural blood in his recent article concerning the obliterative effect of blood in extrapleural pneumothorax. This result is due to the deposition of fibrin and a specific irritative effect of the blood upon the pleura may come into play.

The method used at Olive View is fairly simple. With the patient lying on his back, pneumothorax is attempted in the first and second anterior interspaces (the usual site of cavity puncture is the first interspace). If the usual negative manometric fluctuations of pneumothorax are obtained, a small amount of air is introduced through the needle. If the pressure quickly becomes positive, one has reasonable assurance that he is dealing with a small pneumothorax pocket. If the pressure remains negative the pocket must be of at least fair size. In either event, all the air possible is then sucked out by syringe. An assistant obtains 10 cc. of blood from the cubital vein of the patient on the side opposite to the operation, while the operator keeps his finger over the nub of the pneumothorax needle and holds it very still so as not to move it from its position. The syringe filled with blood is cautiously attached to the pneumothorax needle and the blood slowly injected into the pleural space. If the space is very small, 3 to 5 cc. will suffice. Immediately after the withdrawal of the needle the patient turns and lies prone so that the blood, especially in the case of a larger pneumothorax pocket, will tend to remain in the area where it was first injected. The patient remains prone for several hours after the injection.

Occasionally a pulmonary cavity lies close to the anterior surface of the lung, so that but a narrow layer of atelectatic and caseous tissue separates it from the pleura. Under this circumstance, with the pleural space obliterated, the needle may penetrate into the lumen of the cavity and air is easily withdrawn. It is then easy to be deceived into believing that the pleural space has been entered. The manometric readings could be mistaken for those of a small pleural space because cavity readings fluctuate freely with respiration. But the operator must remember that cavity readings fluctuate usually on both sides of zero, more on the positive side. Moreover, if rapid extraction of air through the needle is attempted, the patient will quickly feel a desire to cough with a distressing tension in the throat and upper chest. Finally, if the patient bears down, the manometer will show a higher positive sweep than if the

needle is in the pleural space. In spite of these precautions, we have on three occasions injected blood into a cavity, with no untoward effect other than a streaked sputum for a little while.

Two weeks has been arbitrarily chosen as the interval before the next check-up, since the changes leading to pleural obliteration brought about by the previous injection should be well established by then. If at the end of that time attempts at pneumothorax at the same site fail to reveal a pocket, the patient is ready for cavity puncture. However, a second physician should repeat the attempt on another day to make doubly sure. If at the time of the first check-up a space is again found, another injection of blood is given in the same way, and this is repeated every two weeks until the space can no longer be found or until it is clear that obliteration by this method will not take place.

We have used this method of pleural obliteration in 9 cases with success; this represents about a third of our cases with cavity aspiration to date. As a rule, more than one injection was necessary in the successful cases; the average was 3. In one case the space failed to close, though 7 injections of blood were given.

At the time of the second or subsequent needling of the pleural space, a small amount of reddish or pinkish serum may be withdrawn. Since this may represent a slight residue from the previous injection of blood, all of the serum possible is withdrawn, and two more weeks are allowed to elapse before the next attempt.

Two patients with pleural obliteration—by this method—subsequently died and were autopsied. The first, a thirty year old Negress, had 4 injections of blood, followed by catheter insertion into the cavity. After two months, the cavity had reduced considerably in size, when the catheter was accidently pulled out and could not be replaced. At about this time, tuberculous enteritis and peritonitis developed and led to her death a month later. Examination of the pleural space after death showed old irregular firm adhesions over the posterior apex which had prevented a previous pneumothorax from becoming effective, plus a well demarcated area of firm adherence (showing no connection with the posterior adhesions) about 6 cm. in diameter directly under the first and second interspaces anteriorly where the blood had been injected. Slightly to one side of the centre of this anterior adherent pleura was the partly healed catheter tract. The remainder of the lung was free of adhesions. This is an example of localized obliteration of a small portion of pleural surface with extensive free pleural space surrounding it.

The second patient, a thirty-five year old Negro who had had numerous profuse haemoptyses previously, had received 5 injections of blood into his pleural space, when the pulmonary haemorrhages recurred with great intensity, initiating a rapid downhill course, terminating in death in six weeks.

Postmortem examination showed complete adherence of the entire pleura, including the injected space.

In this small series, the blood injections appeared to have done no harm. There was no febrile reaction, only minimal discomfort and the adhesions thus formed seemed to be firm and dependable.

SUMMARY

When potential pneumothorax space can be demonstrated in the operative region, single or repeated injections of the patient's own blood may be used to bring about pleural fusion in preparation for cavity puncture.

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PLEURAL ECLAMPSIA DURING ARTIFICIAL PNEUMOTHORAX[1]

ALBERTO DI NEPI

The puncture of the pleura may cause, in rare instances, some general nervous and circulatory symptoms, which may be very serious. Such accidents, though known for a long time, have received more attention in medical literature since pneumothorax therapy has come into general use. The most notorious and serious of these accidents is air embolism, caused by penetration of air into the pulmonary vessels, and from there into the cerebral arteries, or, less frequently, into other arteries. The most outstanding features of the varying symptom-complex known as air embolism are represented by loss of consciousness, circulatory and respiratory deficiency, general nervous manifestations of convulsive or paralytic form, or both; the acute symptoms may be followed by death, or give way to complete and quick recovery; some nervous disturbances, such as localized paralysis, most of them transitory, may sometimes persist after recovery. In almost all cases, except rapidly fatal ones, some localized neurological symptoms appear, as evidence of injury to a circumscribed area of the brain. Sometimes air bubbles are to be found in the patient's retinal arteries (Stargardt (1)), or in the cerebral vessels at postmortem examination, direct evidence of the embolic nature of this syndrome.

Another accident, already known before the introduction of pneumothorax therapy, and later described by Forlanini himself as a complication of pneumothorax, is the so-called pleural eclampsia, caused by a reflex originating in the pleura by irritation and pain of this membrane. This syndrome is similar to the former in symptoms; the most important difference is that motor irritative symptoms more frequently prevail over the paralytic and that localized neurological symptoms are lacking. Fatality in this case is exceptional (if it ever occurs) and the rule is a rapid recovery without any after-effect. These two syndromes, although different in their mechanism, are similar in symptomatology, and in many cases the differential diagnosis between them is impossible. On account of the frequent lack of an exact demarcation between the two syndromes, many authors (Brauer, Spengler, Spielmeyer, Wewer (2), Reyer and Kohl (3) and others) whose experience is based on pneumothorax accidents deny the possibility of pleural eclampsia as a reflex syndrome and ascribe the cases related under

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this name to mild forms of air embolism. I agree with them as to the great importance of air embolism in pneumothorax, and I, too, believe that in the past the diagnosis of pleural eclampsia has been stretched to cover a great number of unlike cases. The fatal cases and those with localized neurological symptoms particularly are really due almost invariably to air embolism. But I believe that pleural eclampsia does undoubtedly exist, even if it is not very frequent. This opinion is shared by many authors (Carpi (4), von Muralt (5), Catler (6) and others). Some authors, such as Capps (8), go even further and point out that pleural reflex is the explanation for the great majority of such accidents and that air embolism can recognized only in exceptional cases. The existence of this form of pleural reflex is proved by the accidents occurring during simple exploratory puncture or thoracocentesis. Chabaud (7) in a review of 114 cases of pleural shock states that two-thirds of the accidents were observed during exploratory or aspiratory puncture, less than one-third during lavage and only a small number during pneumothorax therapy; further evidence is given by some of the accidents that occurred during pneumothorax described by Forlanini and others. Reports of such cases are less common in the recent literature, but they are still to be found; for instance, Capps (8), Sbrozzi (9), Giese and Canway (10) and Fonteyne (11) report 4 cases of pleural eclampsia or shock that occurred during punctures of pleural effusions, but these cases are subject to criticism and objections on account of their fatal end, although postmortem examination failed to support evidence of air embolism. Therefore, I will report the following case, in which, I believe, the reflex mechanism can be proved with the utmost likelihood.

REPORT OF CASE

A. L., a Mestizo, aged twenty-five, was first seen in the Antituberculous Dispensary of Guatemala, on July 10, 1939; he complained of fever, thoracic pain, cough and slight haemoptisis during the previous two years. The clinical and X-ray examination led to the diagnosis of caseous-ulcerative tuberculosis of the entire left lung. The diaphragm on the left side appeared to be almost motionless. His sputum contained tubercle bacilli.

On July 12, 1939, a left pneumothorax was attempted but no satisfactory manometric reading was obtained. A second attempt was made on July 13 with the same result. Thinking that pneumothorax therapy was impossible, or at least very difficult, medical treatment was advised. The patient returned to the Dispensary on October 10, 1939. The clinical and X-ray examination showed slight improvement, but the clinical picture was more or less the same as at the preceding examination. On October 17, 1939, another attempt was made to establish a left pneumothorax; the patient, a strong young man, was not in the least afraid of the little intervention. He was lying on his right side; a needle was inserted in the sixth interspace, on the lateral surface of the

left hemithorax. After introducing the needle, the manometer did not record negative pressure or oscillations indicating the penetration of the needle into the pleural cavity. Therefore, no air was introduced and the needle was quickly withdrawn. During the intervention and the next one or two minutes after withdrawal of the needle the patient felt perfectly well and was very tranquil. Then, the patient, without waiting for the physician's permission, got up, lost consciousness immediately and fell heavily to the floor, with violent tonic convulsions. In this emergency situation the first hurried clinical examination showed the following: tonic contracture of the upper limbs in flexion and of the lower ones in extension; cyanosis of the face; cold sweat all over the body. The pulse rate was considerably slowed but the beat was very strong (both pulse rate and beat had previously been normal). Respirations were slowed and deep. A diagnosis of pleural eclampsia was indicated and immediately an injection of morphine (.01 g.) with cardiazol was given. The convulsive seizure subsided in a few minutes, the general critical condition quickly improved, the cyanosis disappeared, the respiration became calm and regular, the pulse improved, though maintaining a slightly slowed rate with strong beat. The patient remained unconscious, as if sleeping, for more than one hour, during which a second injection of cardiazol was given. Little by little he began to awake, but a sort of mental confusion persisted during the whole forenoon; the patient reacted only to the most violent stimulations and scarcely answered questions. He was admitted to the hospital and spent the whole day and night in a state of drowsiness. On the following morning he felt perfectly well, only moderately weak, was able to walk and was mentally alert. Examination failed to show any neurological or psychic defect. An X-ray examination showed no trace of pneumothorax. The patient was dismissed from the hospital. He was seen again about a month later, his general and local condition was unchanged; during the intervening time he did not complain of any symptom which could be ascribed to the consequences of the accident.

COMMENT

In this case the most important factor, excluding the embolic mechanism and supporting the theory of a reflex mechanism, consists of the occurrence of the accident following simple introduction of the needle without injection of air; the needle was connected with the manometer and the valve that opens the communication to the air reservoir was closed. Furthermore, the needle, as it was withdrawn, was not blood-stained, as it would have eventually been in case of penetration of a vessel; the patient remained very quiet, without coughing or other violent movement apt to cause aspiration of air; the neurological symptoms were of a generalized type, without any symptom of localization; the morphine, apt to interrupt the pathways of a reflex, was apparently

effective immediately; the convulsive seizure subsided promptly and no localized neurological disturbance remained.

A possible objection to the interpretation of this case as one of pleural eclampsia is to be found in the statement of some authors (Brauer (2), Reyer and Kohl (3), Konsislsky (12), Wickler, Marmor and Hast (13)) that air embolism may also occur without actually introducing air from the pneumothorax apparatus; they believe that the negative pressure in the pulmonary venous system may suck air in from the outside, or from the needle and connecting tube, or from the pleural cavity after withdrawal of the needle. I had no opportunity to examine the reports of Brauer's original cases, but I examined the 4 cases reported by Reyer and Kohl (3) in which air embolism occurred, according to the statement of the authors, without introducing air; in 3 cases a pneumothorax was already present before the accident; 2 cases ended in prompt recovery without consequences; therefore, it is doubtful whether it really was an air embolism that had taken place. Only one case ended in death, with postmortem evidence of air in the cerebral vessels; in the fourth case an exploratory puncture was followed by haemoptysis, convulsions and death. Postmortem examination revealed a spontaneous pneumothorax, but no air in the cerebral vessels. Therefore, the cases of Reyer and Kohl (3) cannot be accepted as evidence of spontaneous aspiration of air from the outside. They only demonstrate the possibility of such aspiration from an existing pneumothorax, and I agree on this point. Indeed, if a pneumothorax is present, one can admit that, through a wound in a vein remaining open, air can be driven into a pulmonary vein and actually aspirated, owing to the increased pressure created in the pleural cavity by cough or by strain. But in the case presented no air was introduced from the apparatus, nor did a pneumothorax previously exist. More important is the case of Wickler, Marmor and Hast (13) in which, on the simple introduction of the needle, blood trickled out of it, loss of consciousness and convulsions occurred; recovery ensued, with a consecutive monoplegia which subsided in a few weeks. The accident was ascribed by the authors, with sufficient likelihood, to air embolism to the spinal cord, but anatomical evidence is lacking. The presence of negative pressure in the large branches of the pulmonary veins is commonly admitted, but there is no evidence of negative pressure in the smaller peripheral veins of the lungs, the only ones which can be reached by the pneumothorax needle. In my own experience, in the few cases during an attempted pneumothorax in which the needle surely pierced a vessel, as demonstrated by trickling of blood out of the needle, or by a blood-stained needle after withdrawal or by haemoptysis, I have never observed any symptom by which one could suppose that an aspiration of air into these vessels had occurred. Of course in these cases air was never injected.

Another objection to the theory of pleural reflex was raised by Schlaepfer

(14), based on the results of his experiments in which he failed to obtain any specific reflexes by applying various forms of irritants to the pleura of normal animals and concluded that shock observed in human beings could not originate in the pleura. However, Capps and Lewis (15) made similar experiments on animals with previously induced pleurisy and found that irritation of the inflamed pleura often causes important circulatory reflexes. "These reflexes conform to two types: (*1*) The cardio-inhibitory type, in which the heart is slowed and the pulse tracings make violent excursions with a great range betwen systolic and diastolic pressure. Respirations are usually slowed and may be inhibited. This type of reflex, when it occurs alone, is seldom fatal. (*2*) The vasomotor type, in which the pulse tracings show a steady, rapid decline of pressure, without a great difference in systolic and diastolic pressure; frequently this type terminates in death. Respirations as a rule are shallow and may be rapid" (Capps (8)). It is interesting to note that the symptomatology in my case exactly agreed with the picture of the cardio-inhibitory reflex described by Capps and Lewis (15). These authors exactly describe the nervous pathways followed by both reflexes, as evidence against the scepticism of other authors concerning the physiological basis for a pleural reflex. Besides, the pleura being particularly pain-sensitive (McLaughlin (16)), we may easily understand that it can possibly be the point of origin of a reflex.

Some authors object to the reflex theory, on account of the frequent appearance of the symptoms in the moment of the patient's getting up. According to them, this fact is evidence of air embolism, reaching the cerebral vessels at the moment in which the head rises to a level higher than the trunk. This is not evidence against the reflex theory, because, according to Capps (8), the pleural reflex is exaggerated by the upright position. This explanation seems very plausible, because other reflexes, too, the carotid sinus reflex, for instance, analogous in its manifestations to the pleural one, are exaggerated by the upright position.

Concluding, I believe that the importance of air embolism is not to be undervalued, as some authors (Izzo (17)) think. On the contrary, it always ought to be borne in mind as one of the most dangerous accidents of pneumothorax, and, at the same time, as one which can be avoided, in most cases by using a correct technique. I believe that we must admit the existence of the reflex, pleural eclampsia, even if only in rare instances, of which the reported case is an example.

SUMMARY

A case of pleural eclampsia occurring during an attempted induction of pneumothorax without introduction of air is reported. The various opinions on the mechanism of the nervous and circulatory accidents occurring during

pneumothorax are discussed. The conclusion is that pleural eclampsia, as a reflex syndrome, does really exist, and that accidents of this type cannot in every case be ascribed to air embolism.

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TUBERCULOMA OF THE LUNG[1]

E. MAURER-MAST[2] AND R. MAXWELL FRANKLIN[3]

The following case is reported as an example of an unusual form of pulmonary tuberculosis.

Since only two cases of a similar nature were found in the literature, these cases have been summarized here.

In 1932, Tobias (1) reported the following case: A man, aged fifty-five years, complained of pain of nine months' duration and of increasing severity in the upper part of the left hemithorax. His weight declined forty pounds. Two months before hospitalization, a mass appeared in the left supraclavicular fossa and the overlying skin was soon ulcerated. On admission, Horner's syndrome was present in addition to the mass. There had been no cough, sputum or haemoptysis. Roentgenograms revealed compression of the left upper lobe by a tumor overlying the apex. There was no involvement of the ribs or vertebrae. A bronchogram proved that the tumor was extrapulmonary. Other findings were irregular, constant, low-grade fever; secondary anaemia, rapid pulse and low blood pressure. By exploratory puncture of the tumor, a small amount of pus was obtained and found to contain tubercle bacilli. The patient died of cachexia nineteen months after the onset of symptoms. Tuberculous lesions of the bones of the right hand developed before death.

At necropsy it was seen that the tumor did not involve lung tissue. It arose in the pleura and was adherent to the bony framework of the upper hemithorax, including some ramifications of the brachial plexus as well as the muscles overlying the tumor. The thoracic portion of the tumor was caseous, while the cervical extension was fibrous. The tumor was separated from the lung by pleura and had no capsule of its own. Diagnosis: Primary tuberculoma of the pleura.

In 1936, Norrie, Vivoli and Rey (2) reported a twenty-seven year old man who had been complaining of haemoptyses and retrosternal pain for one year. In the course of time, an enlarged supraclavicular node was removed and found to contain caseous tissue with epithelioid cells. Other findings were dyspnoea, stridor, Horner's syndrome and mild anaemia with leucocytosis. Roentgenograms revealed a large density in the left upper lobe. The Wassermann reac-

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tion was negative and the sputum was negative for tubercle bacilli. At necropsy, the tumor in the left upper lobe was found to be tuberculous. In addition, caseous mesenteric lymph nodes and a miliary seeding of the peritoneum were found.

The report of our case follows: The patient is a Portuguese girl, ten years old, who was brought to Grasslands Hospital on May 4, 1938, complaining of dyspnoea, weakness and loss of weight. Her past history was not pertinent to her present illness, except that she had frequent colds with sore throat. There had been no known contact with tuberculosis. Her illness had begun insidiously six months before admission, with anorexia, loss of weight and dyspnoea on exertion. Dyspnoea increased and three and one-half months before admission she had fever of 103°F. She was in bed then for three weeks.

The patient appeared chronically ill and was five pounds underweight. Her skin was pale and sallow. The cervical lymph nodes were moderately enlarged. The tonsils were hypertrophied and chronically inflamed. The chest was symmetrical. Lungs: on the left, over the area above the third rib anteriorly, the percussion note was dull, breath sounds were bronchovesicular and occasional respiratory wheezes were heard.

Laboratory Data: haemoglobin, 12 g.; erythrocytes, 4.86 millions; sedimentation rate 32 mm. in one hour; leucocytes, 11,650; polymorphonuclear leucocytes, 65 per cent (1 eosinophile, 3 juvenile forms, 7 band forms, 54 segment forms); lymphocytes, 28 per cent; monocytes, 7 per cent. The urine was negative (including examination for Bence-Jones bodies). The sputum and fasting gastric contents were negative for acid-fast bacilli on concentration. The Kline exclusion test was negative. The Mantoux test with Old Tuberculin, 0.01 mg., was positive.

A roentgenogram of the chest, made May 5, 1938, revealed a mass, 7 cm. in diameter and of fairly uniform density, apparently in the upper portion of the left lung. Along the border of this mass there was a light halo of density interpreted as pneumonitis. There were several calcified deposits in both hilum regions. Another film made July 29, 1938 (figure 1) revealed resolution of the halo of pneumonitis and the mass was more clearly defined.

Fever of 103°F. was occasionally experienced. The pulse rate was, on the average, 118 per minute and the respirations were 24 per minute. A nonproductive cough was noticed. There was anorexia and no gain in weight.

On August 8, 1938, a diagnostic pneumothorax was induced on the left (figure 2). By fluoroscopy the mass in the left hemithorax appeared to be above and adherent to the upper portion of the left lung anteriorly and had several thin adhesions to the upper and postero-lateral wall of the chest. There appeared to be a thin pedicle to the mediastinum. A serous pleural effusion appeared in the pneumothorax on September 11, 1938.

On September 27, 1938 the patient was prepared for operation which was

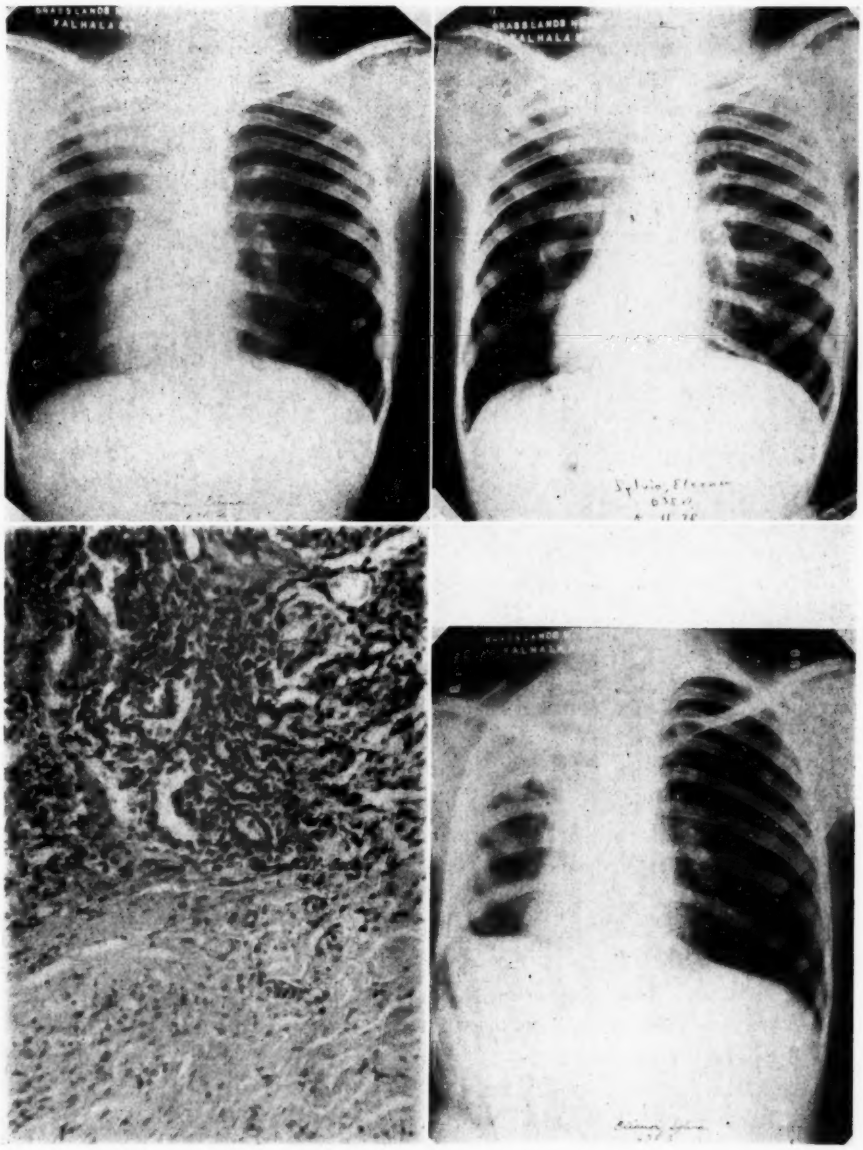

FIG. 1. (Top left.) X-ray film taken on July 29, 1938, showing the condition three months after admission to hospital.

FIG. 2. (Top right.) X-ray film taken on August 11, 1938 three days after induction of pneumothorax.

FIG. 3. (Lower left.) Microscopical section of tumor removed at operation, showing the structure of the tuberculoma.

FIG. 4. (Lower right.) X-ray film taken on March 2, 1939 showing recurrence of infiltrative lesion in upper part of left lung.

performed by Dr. George Adie[4] under endotracheal cyclopropane anaesthesia. The preoperative diagnosis was dermoid cyst. An intercostal incision revealed that the tumor was embedded in the apex of the upper lobe. Pulmonary tissue was dissected from the presenting surface and the tumor had been fairly well freed from the lung when it was ruptured inadvertently and a quantity of gray caseous material was discharged from it. This was carefully removed and the excision of the tumor was completed. The thoracic wound was closed and a drain was inserted through a stab wound in the fifth interspace laterally.

Transfusions were given postoperatively. For three weeks there was fever of a septic type, occasionally reaching 103°F. On the nineteenth postoperative day, thoracentesis on the left yielded 70 cc. of pus. A guinea pig inoculated with this pus was found to have tuberculosis on November 29, 1938. Culture of the pus produced *Staphylococcus aureus*.

The pathologist's report of the tissue removed at operation was as follows: "The tissue is made up of chronic granulomatous and inflammatory tissue containing numerous atypical tubercles and giant cells. A necrotic cavity wall is present. There is no evidence of a dermoid cyst wall. Fat stains reveal no excess lipoid substance and stains for acid-fast bacilli are negative." (See figure 3.)

On the twenty-third postoperative day a course of daily aspirations and irrigations of the left pleural sac with physiological solution of sodium chloride was begun. The temperature returned to normal after one week of this treatment and the pyopneumothorax pocket was obliterated by expansion of the lung by November 13, 1938 (the forty-sixth postoperative day). The wound in the chest wall healed except for two small sinuses. Roentgenograms did not reveal any evidence of involvement of the ribs. Occasional elevations of temperature to 103°F. occurred without return of the empyema. A roentgenogram of the chest made on March 2, 1939 (figure 4) revealed increased density in the upper portion of the left hemithorax.

At the date of this report, April 25, 1940, the sputum remains negative for tubercle bacilli. Discharge from the sinuses in the chest wall ceased Oct. 16, 1939, and they have remained closed. There has been a steady gain in weight and the patient has two hours walking exercise daily. Serial X-ray films have shown gradual clearing and contraction of the density in the left upper third, where light fibrosis remains. The pleura is thickened and the mediastinal contents are drawn to the left.

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SUBCUTANEOUS EMPHYSEMA RELIEVED BY ADMINISTRATION OF OXYGEN[1]

ARTELL E. JOHNSON

The administration of nearly pure oxygen in a variety of conditions has been reported. Fine and his associates (1) first described the accelerated removal of subcutaneous air from animals by this procedure. They applied it clinically with success in gaseous abdominal distention and to those patients with distention of the cerebral ventricles following encephalography. Congdon and Burgess (2) reported 3 patients with subcutaneous emphysema who were benefited by administration of 95 per cent oxygen.

Theoretically, any nitrogen reservoir in the body such as that in the bowel following obstruction, in the cerebral ventricles after encephalography, in the tissues in subcutaneous emphysema or the nitrogen in solution in fat should be rapidly dissipated as the result of continuous or nearly continuous inhalation of an atmosphere high in its oxygen content. This is due to the washing of nitrogen out of the alveoli and replacement by oxygen. As the process goes on, the nitrogen in physical solution in the body tissues will be eliminated gradually, being carried from the tissues to the lungs through the blood stream and finally diffusing into the alveoli. The resultant lowered nitrogen tension in the tissues permits diffusion of nitrogen from the reservoir into the tissues from which it likewise will be carried away for excretion through the lungs. Oxygen and carbon dioxide, when present in a free gas in the body—as in pneumothorax—are quickly brought into equilibrium with the tissue pressures of these gases (30 mm. of mercury for oxygen, 45 to 50 mm. for carbon dioxide). This corresponds approximately to 3 per cent of oxygen in the total gas volume and 7 per cent of carbon dioxide. If there is no free inert gas present, such as nitrogen, the oxygen and carbon dioxide are absorbed completely. This was well demonstrated on animals by Campbell (3) and is a common clinical experience. Thus, a method of removing the residual nitrogen is of definite value in cases of massive subcutaneous or mediastinal emphysema. The following case report is illustrative of the successful alleviation of symptoms in such a case.

A. M., age twenty-two, a housewife of Italian extraction, had had symptoms

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of open pulmonary tuberculosis for four weeks with pulmonary bleeding for three days prior to entry at Bellevue Hospital on March 15, 1940. One week later, a left artificial pneumothorax was instituted to control an excavating tuberculous lesion in the upper left lung field. The course was favorable until the thirty-fifth day of pneumothorax when the patient was given a refill of 300 cc. of room air as on previous occasions. Pleural pressures before were −8, −3, as against −5, −2 following this procedure. No reaction was noted during administration of air and there seemed to be no obstruction to the flow of air. At this time there was a 30 per cent collapse of the lung and, therefore, it was not likely that the patient had sustained a tear of the visceral pleura. Immediately after the withdrawal of the needle, however, an episode of continuous small, tensely forced coughs began which lasted throughout the day. Within an hour she began complaining of pain in the throat and of dysphagia, and shortly thereafter a fairly massive subcutaneous emphysema was noted in the left axilla and on both sides of the neck. This rapidly became sufficiently marked to obliterate the normal neck contours and local pain was greatly accentuated.

Fluoroscopy demonstrated the emphysema of axilla and neck but failed to show any gas in the mediastinum. An X-ray film confirmed the fluoroscopic findings and indicated that the mediastinum was not displaced. No gas could be seen in the mediastinum although it is not felt that mediastinal emphysema can be entirely ruled out on this basis. Pleural readings repeated at this time were −8, −5, notably less positive than at the end of air administration earlier. In view of this, it was suggested that air was escaping from the pleural space through the needle puncture. This was further indicated by the fact that the major pocket of gas was about the puncture site in the left axilla. It was concluded that the air then travelled along tissue planes into the cervical region where, at least superficially, it may cross the mid-line to the opposite side. There was no emphysema over the right thorax.

By evening the patient was in great distress. The temperature was 105°F., respirations, 44 per minute. The cough was somewhat less annoying following large dosage of sedatives but it still persisted as small paroxysms. She complained of marked pain in the neck and on swallowing. Because of the prominence of the symptoms and the apparent need for some immediate therapy, a pressure pad was tightly applied to the needle sites to prevent further escape of gases from the pleural space and high concentration of oxygen was administered direct from a tank by means of the B-L-B (Boothby, Lovelace and Bulbulian) mask. This was continuous except for a thirty minute rest-period every five or six hours to allow for taking food and nursing care. No procedures were carried out other than heavy sedation.

Following this there was in all respects a prompt response. By the next morning, fourteen hours later, the temperature had fallen nearly to its previous

level (102.4°F.), respirations were 22 per minute and the dysphagia and neck pain had ceased. About 80 per cent of the emphysema of neck and axilla was estimated to have disappeared and normal neck contours had been restored. A chest roentgenogram on this day, taken about twenty-two hours after the film of the previous day and eighteen hours after oxygen administration, failed to show any evidence of gas in the tissues of thorax or neck; this was in marked contrast to the large masses of gas over the left thorax and both sides of the neck visible in the previous X-ray film. In spite of these X-ray

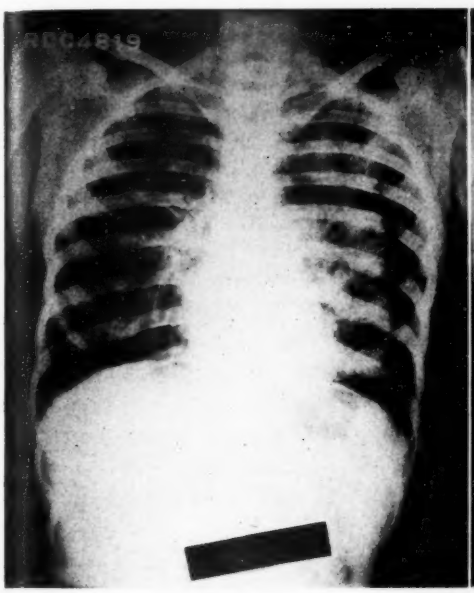

FIG. 1

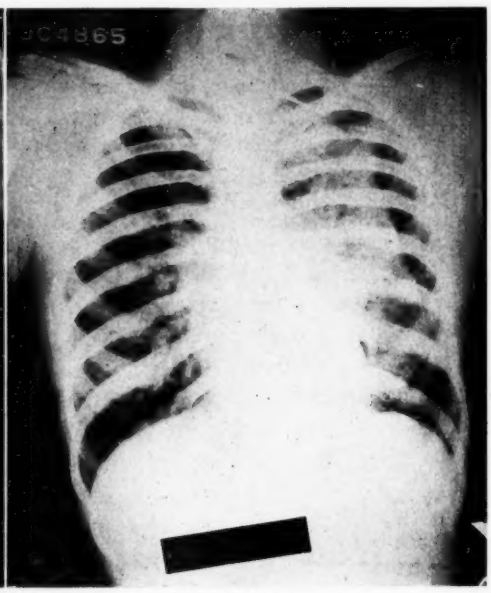

FIG. 2

FIG. 1. X-ray film of chest taken at the time of the most severe symptoms, showing much gas in the subcutaneous tissues of left hemithorax and both sides of the neck.

FIG. 2. Chest film of the same patient taken twenty-two hours later, showing the rapid disappearance of the subcutaneous gases following inhalation of nearly pure oxygen.

findings, small traces of gas in the tissues could be detected by palpation and by auscultation for as long as thirty-six hours. At this time, the oxygen administration was discontinued. No further therapy was deemed necessary although the pressure pad remained in place for a short time as a precaution against escape of any additional gas from the pleural cavity. It is of interest that the cough which probably had originally caused the emphysema disappeared when the other symptoms became less intense. It is possible that each tended to aggravate the other and thus constituted a cycle of ever increasing symptoms. No explanation is available for the sudden elevation

of temperature nor its recession following the acute episode. No pleuritis occurred at this or subsequent date, as evidenced by blood count or pleural fluid. The patient's course with continued pneumothorax was entirely uneventful as long as she remained at this hospital.

SUMMARY

The administration of nearly pure oxygen as a means for removing nitrogen accumulations in the body has previously been successfully employed. A case of severe subcutaneous emphysema is reported in which prompt alleviation of symptoms in a short period of time was obtained by this procedure.

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CULTURE OF TUBERCLE BACILLI[1]

An Improved Technique

W. STEENKEN, JR. AND M. M. SMITH

In a previous publication (1), we showed that a medium which contained a bacteriostatic dye not only inhibited the growth of some of the secondary organisms, but also that of the tubercle bacillus; that digestion with either sodium hydroxide or sulphuric acid was apt to inhibit the growth of tubercle bacilli in material containing small numbers of these organisms; and that the growth was more luxuriant on a medium of pH 6.2 than on one of pH 7.2. Because of these findings, we (2) suggested the substitution of nonbacteriostatic concentrations of lacmoid for malachite-green in the preparation of Hohn's medium and an adjustment of the pH to 6.2.

Many times, specimens that were negative for tubercle bacilli by smear showed a growth on our modified medium, whereas none occurred on Hohn's, and only occasionally did we see growth on Hohn's medium when none developed on the modified medium. A growth of tubercle bacilli on our modified medium appeared earlier than on Hohn's or any other medium containing a bacteriostatic dye. But when cultivating sputum, urine, gastric contents or other contaminated material, we had many more contaminations on the modified medium than on Hohn's, or any other medium embodying a bacteriostatic dye.

To reduce the number of contaminations on our modified medium and at the same time avoid the effect of prolonged contact with a bacteriostatic dye, the following procedure has been followed for culture from sputum, pleural and gastric fluids. For culturing urine it was necessary to employ preliminary sedimentation (3).

METHOD

A fifty-hour sputum specimen is collected in a 100 cc. widemouthed bottle, stoppered with a good grade of cork. An equal volume of 4 per cent sodium hydroxide is added, and the mixture homogenized for ten minutes in a shaking machine,[2] followed by one hour's incubation at 37.5°C. It is then centrifuged for ten minutes at high speed in sterile pyrex tubes which have been sealed with sterile rubber caps (type used for capping babies' milk bottles). The sediment is neutralized with normal hydrochloric acid containing 10 per cent

[1] From the Research and Clinical Laboratory, Trudeau Sanatorium, Trudeau, New York.

[2] Seven hundred and sixty-three dimensional shakes per minute. (Machine to be introduced by Will Corporation.)

by volume of phenol-red indicator, and adjusted on the acid side to a pH of about 6.4 (it is best to approach the final pH with either N/10 hydrochloric acid or N/10 sodium hydroxide as may be required).

This suspended sediment is divided into three equal portions. Two of these portions are transferred to two small vials with round bottoms that will stand centrifuging and which can be stoppered with small corks. (Small round bottom 5 cc. vaccine vials are well suited for this purpose.) To one vial, 5 cc. of a 1 to 1,000 solution of malachite-green is added and to the other vial, 5 cc. of a 1 to 10,000 solution. The third vial is kept as a control. The vials which contain the dye are then stoppered and agitated in the shaking machine for ten minutes, then centrifuged for ten minutes at high speed, and the supernatant fluid pipetted off with a sterile capillary pipette. The sediment is then suspended in 1 cc. of sterile distilled water.

For purposes of comparison these suspensions, including the control without dye, were each inoculated on two tubes of the modified medium and two tubes

TABLE 1

Results of culture of 114 sputum specimens after digestion with 4 per cent sodium hydroxide

	CONTAMINATIONS IN PER CENT				GROWTH OF TUBERCLE BACILLI			
	Complete		Partial		Positive cultures in per cent		Average number of days for growth	
	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.
Malachite-green 1:1,000.....	0	0	0	0	9.7	15.8	28.7	23.2
Malachite-green 1:10,000.....	0	0	1.8	1.8	11.4	18.4	24.7	20.2
Controls.....	4.4	16.6	5.3	16.6	14.9	16.7	25.5	22.6

of Hohn's; thus making a total of twelve tubes planted: four with inoculum free of dye; four with inoculum containing 1 to 1,000 malachite-green and four with inoculum containing 1 to 10,000 malachite-green.

Table 1 gives the results of 114 sputum specimens cultured by this technique on Hohn's and on Steenken and Smith's (S. & S.) medium.

Table 1 shows that preliminary treatment of material for culturing with 1 to 1,000 or 1 to 10,000 malachite-green solution reduced the percentage of contaminations without inhibiting the growth of tubercle bacilli. This reduction is most impressive on the S. & S. medium. It will also be noted that there is a greater number of positive cultures of tubercle bacilli on the modified medium than on Hohn's, whether the sediment had been treated or untreated with dye. Growth is observed earlier on the S. & S. medium than on Hohn's medium.

Tubes were considered partially contaminated if the amount of contamination did not interfere with the growth of tubercle bacilli.

As the digestion of material with 4 per cent sodium hydroxide solution more

or less inhibits the growth of tubercle bacilli (1), we thought that by reducing the concentration of sodium hydroxide to 2 per cent, we would still get good digestion, but less inhibition of the growth of tubercle bacilli. We felt that contaminating organisms could be controlled by preliminary treatment of the sediment with malachite-green.

Table 2 shows the results.

On comparing table 2 with table 1, it is evident that, with preliminary 2 per cent sodium hydroxide digestion, there are a few more contaminations on the S. & S. medium than on Hohn's medium. Table 2 also shows a greater percentage of positive cultures on both media. Again growth is observed earlier on the S. & S. medium. For sputa and other specimens where there are from 5 to 15 cc. of material to be digested, and when they are not too tenacious and heavily contaminated, preliminary digestion with 2 per cent sodium hydroxide can be recommended.

TABLE 2

Results of culture of 114 sputum specimens after digestion with 2 per cent sodium hydroxide

	CONTAMINATIONS IN PER CENT				GROWTH OF TUBERCLE BACILLI			
	Complete		Partial		Positive cultures in per cent		Average number of days for growth	
	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.
Malachite-green 1:1,000.....	0	5.2	0	0.8	14.2	17.1	28.1	23.7
Malachite-green 1:10,000.....	1.5	4.5	1.5	1.5	17.1	20.9	26.1	23.4
Controls.....	3.7	26.1	9.0	11.9	25.4	20.1	25.3	23.6

URINE

Table 3 gives a summary of the results obtained by culturing 51 twenty-four-hour specimens of urine. These specimens were sent in to the laboratory for culture of tubercle bacilli because of the presence of albumin or pus cells.

Procedure: A twenty-four-hour urine specimen is collected in the usual manner, and for every 100 cc. of urine, 1 cc. of protein suspension (3) is added. The resulting mixture is allowed to stand in an icebox for twenty-four hours. By that time, most of the protein will have sedimented to the bottom of the bottle, carrying tubercle bacilli with it. The supernatant urine is then syphoned off, and the sediment is centrifuged at high speed for ten minutes to free it of residual urine. This sediment is then digested in the usual manner with 4 per cent sodium hydroxide and subjected to the action of the two dilutions of malachite-green as above.

From the results shown in table 3 it is evident that the urine treated with the more concentrated dye gives rise to the least number of contaminations. The number of positive cultures of tubercle bacilli were too few to make any comparison of the advantages of one or the other medium.

The type of contaminating organisms in urine cultures is quite different from that in sputum or pleural fluid cultures, in that the contaminating organisms from urines spread and involve the whole slant.

PLEURAL FLUID

Most of the pleural fluids that were cultured were not secondarily infected, but those that were, we treated in the same manner as the specimens of sputa and with equally good results as shown in table 4.

TABLE 3

Results of culture of 51 specimens of urine after digestion with 4 per cent sodium hydroxide

	CONTAMINATIONS IN PER CENT				GROWTH OF TUBERCLE BACILLI			
	Complete		Partial		Positive cultures in per cent		Average number of days for growth	
	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.
Malachite-green 1:1,000.....	3.9	0	2.0	0	3.9	3.9	21.0	18.5
Malachite-green 1:10,000.....	17.6	13.7	0	5.9	2.0	2.0	19.0	19.0
Controls.....	49.0	60.8	0	2.0	2.0	2.0	16.0	16.0

TABLE 4

Results of culture of 28 specimens of pleural fluid after digestion with 4 per cent sodium hydroxide

	CONTAMINATIONS				GROWTH OF TUBERCLE BACILLI			
	Complete		Partial		Positive cultures		Average number of days for growth	
	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.	Hohn's	S.&S.
Malachite-green 1:1,000.....	0	0	0	0	15	19	27.34	22.90
Malachite-green 1:10,000.....	0	0	0	0	15	19	23.88	18.81
Controls.....	0	1	0	0	19	18	19.41	15.61

GASTRIC CONTENTS

In 57 gastric content cultures we had very convincing results from the treatment of digested material with the dye. There were 11 cultures that showed complete contamination on S. & S. medium before treatment with the dye and none after treatment. Fourteen of these cultures had positive growth for tubercle bacilli.

DISCUSSION

We have shown that the addition of 5 cc. of malachite-green, in concentrations of 1 to 1,000 or 1 to 10,000 to the digested sediment of sputum, urine, pleural fluid or gastric contents will bring about a substantial decrease in con-

taminations in cultures. Since contamination is a serious obstacle for successful culture technique, we feel that anything that tends to eliminate contamination, without affecting the growth of the tubercle bacillus, should be of interest.

It is convincing that the malachite-green incorporated in Hohn's medium prevents many more contaminations than the lacmoid in the modified medium. However, after sediments are treated with malachite-green 1 to 1,000 or 1 to 10,000, the encouraging reduction in the number of contaminations on the modified medium is striking when compared with the controls, and causes the modified medium to compare very favorably with Hohn's.

There was also a higher percentage of positive cultures of tubercle bacilli on the modified medium than on Hohn's. This improvement is undoubtedly due to the absence of a bacteriostatic dye in the modified medium and to the pH adjusted to 6.2.

Finally, growth was consistently observed earlier on the modified medium than on Hohn's medium.

If the number of contaminations can be reduced to a low percentage, and the medium still shows a 2 to 3 per cent increase in positive cultures and a four to five-day earlier growth over other methods, a definite improvement is made in technique. Until discovery of a growth promoting substance that will shorten the lag or growth period of the tubercle bacillus, or until discovery of a new digestant to break up materials, kill secondary organisms and not affect the growth of the tubercle bacillus, we cannot expect a more rapid growth of the tubercle bacillus in culture than we have at present. Our experience with this technique shows that we should use less destructive agents in the preparation of our materials for culture and smear; that the culture medium should have an optimum pH for the growth of the tubercle bacillus and that bacteriostatic substances should be eliminated from the medium.

Those familiar with culture work know that it is very easy to grow tubercle bacilli from frankly positive specimens, but to grow tubercle bacilli from specimens which are negative by smear is a more difficult matter. If such specimens are cultured on two different media, using three slants of each, one or two colonies may appear on one or two tubes of one medium and none on the other. Such findings suggest the planting of material on two media which promote a good growth of tubercle bacilli—one medium adjusted to pH 6.2 and the other to pH 7.2. High and low pH's will often offset poorly adjusted inoculum, a medium of pH 6.2 compensating for a slightly alkaline inoculum and a medium of pH 7.2 compensating for a slightly acid inoculum.

REFERENCES

(1) Steenken, W., Jr., and Smith, M. M.: Am. Rev. Tuberc., 1938, *38*, 305.
(2) Steenken, W., Jr., and Smith, M. M.: Ibid., 1938, *38*, 514.
(3) Steenken, W., Jr.: To be published.

STATISTICAL DATA

Edited by JESSAMINE S. WHITNEY

INCIDENCE OF TUBERCULOSIS IN AUSTRALIAN ARMY RECRUITS

Between December 23, 1939 and March 1, 1940, 22,000 recruits for the 6th Division of the Australian Imperial Force were X-rayed, using 35 mm. film.[1] No case was diagnosed on this basis alone, however, but a 14 by 17 inch film was taken of all suspects. Out of the 22,000 men X-rayed, 109 had active pulmonary tuberculosis, undetected by the general medical examination. This is an incidence of just under 0.5 per cent. In some cases, even when films revealed extensive lesions with cavities and sputum examination or the fasting-stomach contents revealed tubercle bacilli, no physical signs of disease could be found.

HOW TUBERCULOSIS ASSOCIATIONS CAN AID IN DEFENSE PROGRAM

The New Hampshire Tuberculosis Association furnished the necessary personnel for taking medical histories and X-rays to examine one regiment of the New Hampshire National Guard when the members of that regiment were called into federal service.[2]

Out of 1,552 officers and enlisted men, chest X-ray films revealed 7 cases of parenchymal tuberculosis, all minimal. This is an incidence of less than 0.5 per cent, or 4.5 per thousand. The total cost of finding these 7 cases was $2,794.35 or $1.80 per man examined, and about $400 per case found.

As the authors point out: "With a tour of active military service facing them, it was quite important to these men that their cases of minimal tuberculosis be detected and that they be spared the exertions of the coming year. It was equally important to the army that these men should not remain to serve as foci of infection to the men quartered with them."

The X-raying was done during nine days, concurrently with regular physical examinations, and with serological tests of the blood and urinalyses.

COST OF TUBERCULOSIS COMPENSATION TO WORLD WAR VETERANS

Dr. Ramsay Spillman writing[3] in the Journal of the American Medical Association, has given us a very timely summary of the cost of tuberculosis

[1] Eric L. Cooper: Pulmonary Tuberculosis in Recruits, British Medical Journal, August 24, 1940.

[2] Travis P. Burroughs and Alfred L. Frechette: Cooperation of Health Agencies with Army Authorities, Journal of the American Medical Association, October 26, 1940.

[3] Ramsay Spillman: The Value of Radiography in Detecting Tuberculosis in Recruits, Journal of The American Medical Association, October 19, 1940.

in the A.E.F. following the first World War. Taking into account actual reports of the United States Government and making allowance for costs that are not apparent, the author estimates that the cost of taking a man who has tuberculosis into the service has been somewhere around $10,000 per man, to date.

This figure becomes more significant when compared with the figure in the preceding note, which gives the cost of discovering tuberculosis in a recruit and rejecting him from service, which amount is $400. The moral is clear. The author sums it up as follows:

"A normal chest roentgenogram should be the criterion of acceptance in a future mobilization, including the proposed draft for training, and it should be made and reported before the recruit has spent a night away from his own roof to obviate a repetition of the claims for aggravation of preëxisting tuberculosis which occurred during and after the World War."

TUBERCULOSIS DEATH RATE CONTINUES ITS DECLINE

Preliminary figures furnished by thirty-one states and the District of Columbia to the United States Public Health Service[4], for the first six months of 1940, show that the tuberculosis death rate in that period is 1.8 per cent less than the rate for the corresponding period in 1939. Confirmatory evidence is also furnished by a report[5] on tuberculosis mortality in New York City which shows for the first nine months of 1940 a decline of 3.4 per cent in the tuberculosis rate over the corresponding period in 1939.

LITTLE TUBERCULOSIS AMONG CEMENT WORKERS

A reprint[6], recently come to this desk, indicates the enterprise and interest in health matters of the Portland Cement Association. Because of the association of lung disease with work in industries in which there is exposure to siliceous materials, that Association undertook, through the Saranac Laboratory for the Study of Tuberculosis at Saranac Lake, New York, to determine to what extent tuberculosis was prevalent among workers in that industry.

The study included 2,278 men, at least 7 per cent of the total employed force of the industry, constituting the entire personnel of eleven widely

[4] Provisional Mortality Rates for the First Half of 1940, Public Health Reports, November 1, 1940.

[5] Compiled from reports, by courtesy of the Department of Health, City of New York, by G. J. Drolet, New York Tuberculosis and Health Association, 386 Fourth Avenue, New York City.

[6] Leroy U. Gardner, Thomas M. Durkan, Daniel M. Brumfiel and Homer L. Sampson: Survey in Seventeen Cement Plants of Atmospheric Dusts and Their Effects upon the Lungs of Twenty-two Hundred Employees, The Journal of Industrial Hygiene and Toxicology, September, 1939.

separated and representative plants, extending from New York to California and from Michigan to Alabama and Texas.

Each worker had a physical examination including a detailed occupational case history and each had an X-ray examination. Studies were made to determine the chemical content of dusts encountered in each of the various plants. The atmospheric conditions in the various departments of the industry were also studied in great detail.

Ages of employees, length of service and racial composition of the group were carefully considered. Eighty-five per cent of the entire group were white males eighteen to eighty years of age. Nearly half were forty or over and nearly one-fourth were fifty or more years of age. The duration of employment for the exposed group shows that over 55 per cent had been employed ten years or more and 32 per cent for fifteen years or more.

For purposes of analysis the employees were separated into two groups, the first comprising 1,979 exposed to more or less dust in their occupations, and 299 office and laboratory workers, machinists, watchmen and others not often in contact with cement plant dusts. Of the exposed group, 82 per cent showed no abnormality of any kind in the roentgenogram, 17.5 per cent had "linear exaggeration" of some degree and only 0.4 per cent showed silicotic nodulation. In the entire group of 2,278 employees only 4 instances of active tuberculous disease were discovered. The authors conclude that:

"The incidence of tuberculosis and other chronic infections of the lungs was found to be less than that in the general population. The manifestations of tuberculosis occurred in typical form and at the same age periods as in persons not exposed to dust by occupation. It is concluded that prolonged inhalation of cement dust has no unfavorable influence upon susceptibility to tuberculous infection or upon its subsequent evolution."

AMERICAN TRUDEAU SOCIETY

Dr. John B. Barnwell, University Hospital, University of Michigan, Ann Arbor, is Chairman of the Committee on Nominations for officers and Council members of the American Trudeau Society. The other members are Dr. P. A. Yoder, Forsyth County Sanatorium, Winston-Salem, North Carolina, and Dr. Sidney J. Shipman, 490 Post Street, San Francisco, California.

The Committee asks members of the Society to send them nominations for President-elect, Vice-President and Secretary-Treasurer, as well as for five members of the Council, the latter to serve three years.

The Committee will submit its report at the Business Session on May 5, 1941, to be held at the Hotel Gunter, San Antonio, Texas.

OLEOTHORAX[1, 2]

A New Evaluation with a Review of One Hundred and One Cases

R. H. BROWNING, C. C. DUNDON AND E. S. RAY

Oleothorax has been used in the treatment of tuberculosis since introduced by the French physician, Bernou, in 1921. Despite this fact, there is still considerable uncertainty in America as to its value. Many questions remain with regard to indications, contraindications, technique of administration, complications and results to be expected.

The literature on this subject in English is limited and cases reported are few. While the field of oleothorax therapy is and should be restricted to a relatively small number of cases, we feel that even this group is not generally receiving its benefits. For these reasons it has seemed worth while to present this additional series of 101 consecutive cases in which oleothorax was instituted for disinfection or inhibition purposes during the seven and one-half year period between December, 1931 and July, 1939. Four per cent gomenol in cottonseed oil was used in empyema cases, and 1 per cent gomenol in cottonseed oil for patients with obliterative pleurisy, except those who had a concomitant empyema. This latter group received the 4 per cent mixture. In this connection we feel that other case reports adequately demonstrate that olive oil and mineral oil are satisfactory for oleothorax. Mineral oil because of slow absorption is probably superior to any, when used for inhibition purposes.

The 101 cases of this study all had oleothorax induced at Sunny Acres Sanatorium and have been cared for in sanatoria, out-patient clinics or by private physicians since that time. With the exception of 9 who have died and 2 who could not be located, recent reports of condition and work capacity were obtained in every case. Of a total of more than 1,300 pneumothorax cases treated during the period, only 101 received oleothorax.

A brief study is included of 21 other cases in which oleothorax was used in connection with extrapleural pneumothorax.

[1] From Sunny Acres, the Cleveland Tuberculosis Sanatorium, Warrensville, Ohio.

[2] Presented at Clinic No. 2 of the Medical Clinics at the 35th annual meeting of the American Trudeau Society, Cleveland, Ohio, June 4, 1940.

INDICATIONS

There have been two predominant indications for oleothorax therapy. These are:

1. Persistent pure tuberculous empyema, complicating artificial pneumothorax—"disinfection oleothorax."
2. Progressive obliteration of the pleural space in the course of a desirable artificial pneumothorax—"inhibition oleothorax."

A number of other uses have been suggested, including the further collapse of lungs inadequately collapsed by pneumothorax, the treatment of persistent serous effusions, the treatment of small bronchopleural fistulae, the stiffening of a too flexible mediastinum and the treatment of mixed infection empyema. Only the first two indications have been given much consideration in this study, and the only 2 cases receiving oleothorax for indications other than tuberculous empyema or obliterative pleurisy have been omitted.

It has been our feeling that oleothorax is contraindicated in both mixed infection empyema and bronchopleural fistula and that these conditions are primarily surgical problems. However, rather extensive use of oleothorax in the treatment of mixed-infection empyema has been made at the Matson Clinic (1). Successful results have been attained and the procedure is still being used.

Of the 101 cases (table 1), 77 were of the white and 24 of the colored race; ages ranged from thirteen to fifty-two years, with the largest group (46) in the age group twenty to twenty-nine years.

EXTENT OF DISEASE

Many patients had extensive bilateral disease, but all were thought at the time treatment was started to have at least a fair prospect of eventual recovery. Various forms of supplementary treatment were used, both on the oleothorax side and on the contralateral side. These and further details of the extent of the tuberculous disease present before collapse therapy was started, are shown in table 2.

TECHNIQUE

This paper does not attempt to discuss technique in detail (1, 2); however, several points are worthy of comment. Throughout this entire series it was our practice, after careful test doses, to fill the existing pleural space completely with oil within three to six weeks of the first

TABLE 1

Indications and extent of disease

Age—Race

	TUBERCULOUS EMPYEMA	OBLITERATIVE PLEURISY
Minimal	0	0
Moderately advanced	23	27
Far advanced	25	26
Total	48	53
AGE		
10–19	7	14
20–29	24	22
30–39	9	12
40–49	5	5
50–60	3	0
Total	48	53
COLOR		
White	37	40
Colored	11	13
Total	48	53

TABLE 2

Distribution of lesions before collapse therapy; supplementary therapy

INDICATION FOR OLEOTHORAX	TOTAL	INVOLVEMENT		THERAPY		
		Parenchymal disease	Cavity	Pneumothorax	Pneumonolysis	Phrenic Paralysis
Oleothorax side						
Tuberculous empyema	48	48	48	48	21	10
Obliterative pleurisy	53	53	53	53	16	17
Total	101	101	101	101	37	27
Contralateral side						
Tuberculous empyema	48	35	5	5	3	3
Obliterative pleurisy	53	30	9	11	5	5
Total	101	65	14	16	8	8

instillation. This was done despite the persistent formation of small amounts of purulent fluid in many cases. All pleural exudate was aspirated at the time of each oil instillation, and patients who were

forming fluid were carefully watched for signs or symptoms of positive intrapleural pressures.

Patients forming more than 50 cc. to 75 cc. of pus per week either did not receive oleothorax at all, or were only partially filled with oil—a good-sized cushion of air being left to prevent the development of excessive pressures.

We were able to demonstrate repeatedly in treating the empyema group that a partial oleothorax, while it might result in some thinning of the fluid and less rapid fluid formation, was frequently not effective in stopping fluid formation completely; however, when a complete oleothorax was instituted, results were much better and success more frequent.

Complete filling in the presence of fluid formation may seem dangerous on theoretical grounds and has been critized; however, in our hands there have been no serious results, as may be noted in the discussion of complications which follows. The amount of oil required for complete filling in the empyema group varied from 300 cc. to 2,800 cc. with an average of 1,135 cc. In the group with obliterative pleurisy, the amounts required varied from 100 cc. to 2,500 cc. with an average of 908 cc. Eighteen-gauge needles were used throughout the entire period of the study.

MAINTENANCE OF OLEOTHORAX

The selection of cases, the testing of the pleura, the induction of oleothorax and the early months of treatment require good judgment and the exercise of careful supervision and frequent observation. In most patients, however, the maintenance of a successful oleothorax, once established, is a relatively simple matter.

When complete oleothorax is established, it is our custom to check the oil every three months in most cases. However, patients still forming fluid or in whom oil absorption is unusually rapid are treated more often. The routine of treatment consists of a fluoroscopic examination followed by needle puncture at the lowest part of the pocket with the patient sitting. This is to determine the presence or absence of exudate. Aspiration of any exudate present is performed. The patient then lies on his untreated side and oil is injected in small quantities until it begins to return through the needle when the syringe is removed. It is our aim to leave pressures as nearly neutral as possible.

The size of refills after a three-month interval has ranged from 0 cc.

to 140 cc. In a number of cases, serial X-ray studies have revealed a gradual contraction of the oleothorax pocket with reëxpansion of the lung. This tendency toward reëxpansion results in the development of positive pressures in some cases, as has been demonstrated by observing pressures after a three-month interval. In several cases in which pressures had been left neutral, positive pressures developed, even though there was no fluid formation in the interval.

We have had opportunities to observe several patients with successful oleothorax who started to form either serous or purulent fluid under the oil. Fever, malaise or mild pressure symptoms developed in some, but most of these were promptly relieved by aspiration, and the duration of symptoms was quite short. In other cases, the amount of fluid was small and the patients had noticed no symptoms. In a few cases recurrent fluid formation became excessive and oleothorax had to be abandoned.

EARLY RESULTS AND COMPLICATIONS

Empyema: All of the 48 empyema cases had had serous effusions which passed through the seropurulent stage to the frankly purulent stage. All had been treated by repeated aspiration for varying periods of time, and in addition many of them were subjected to other therapy, including saline or sodium citrate irrigation, instillation of metaphen in oil, merthiolate or azochloramid. While occasional brilliant results were obtained with one or another of these methods, none of them was consistently effective. Oleothorax was never started when there was any feeling that the empyema would respond to any of these other forms of therapy or to aspiration alone. Thus, only the more severe and persistent cases received oleothorax. The average duration of fluid formation before oleothorax for the entire empyema group was five and one-half months, with a range from one month to twenty-eight months.

Oleothorax was never induced when the patient was acutely ill or toxaemic, and all but one of our cases had reached a relatively afebrile stage before oil instillation was begun. Considerably more than half of the empyema cases had easily demonstrable tubercle bacilli in the pleural exudate, and the finding of these organisms after several negative examinations was, at times, the signal to induce oleothorax. None of the cases receiving oleothorax showed clinical or laboratory evidence of secondarily infected pleurae.

The criterion of success in the empyema group was cessation of the

formation of pleural exudate. All cases studied had had oleothorax for at least six months, and the longest period of treatment was more than eighty-four months. Examination of the early results of oleothorax therapy in the treatment of tuberculous empyema (table 3) shows that success was attained in 36 (75 per cent) of 48 patients, all within a period of twelve months from the first instillation.

TABLE 3

Early results and complications; empyema group

TYPE OF FLUID AND PERIOD OF FORMATION AFTER OLEOTHORAX WAS STARTED	NUMBER OF CASES
Successful cases	
Exudate stopped at once	6
Seropurulent fluid less than 2 months	4
Purulent fluid less than 2 months	15
Seropurulent fluid less than 6 months	4
Purulent fluid less than 6 months	5
Purulent fluid less than 12 months	2
Total of successful cases	36
Unsuccessful cases	
COMPLICATION	
Persistent purulent fluid	8
Bronchopleural fistula	2
Pleurocutaneous fistula	2
Total of unsuccessful cases	12

Of the remaining 12 cases, 8 were considered unsuccessful because of persistent purulent fluid. The outcome of these cases is as follows:

1. Oil aspirated after four months. Successful thoracoplasty performed.
2. Oil aspirated after three years. Successful thoracoplasty performed.
3. Oil aspirated after twelve months. Successful thoracoplasty performed.
4. Oil tried without success for eight months. Patient had bilateral tuberculous empyema and died of amyloid disease, the only diagnosed case of amyloid disease in the entire series.
5. Oil tried for four months. Patient then died of acute miliary tuberculosis.
6. Oil aspirated after five months. Fluid formation stopped spontaneously, and patient now has a dry pneumothorax pocket.
7. Fluid still forming after ten months; oleothorax is being continued and may yet be successful.

8. Had persistent fluid formation after many months of oleothorax. Oil was aspirated and empyema treated by aspiration and irrigation. Patient refused thoracoplasty repeatedly, finally developed a bronchopleural fistula some time after oleothorax was terminated. He became secondarily infected, and has now received open drainage preparatory to thoracoplasty.

Two cases developed bronchopleural fistula:

1. Fistula developed soon after a refill during which the operator was conscious of needling the lung. Oil was aspirated and no secondary infection occurred. A successful thoracoplasty was performed.
2. Patient had stopped forming pus after ten months of oleothorax. She then left the Sanatorium without approval and eight months later developed a fistula with secondary infection. After rehospitalization, open drainage was performed. Extension of disease in the opposite lung prevented thoracoplasty. Patient again left without approval, and died at home some months later.

Two cases developed pleurocutaneous fistula:

1. Fistula developed after five months of successful oleothorax. Oil was aspirated, fistula healed and a satisfactory pneumothorax was maintained.
2. Fistula developed after nine months of oleothorax. Oil was aspirated. Fistula healed, but exudate still forms without secondary infection and oleothorax will be attempted again.

In addition to the surprisingly prompt cessation of fluid formation seen in many cases, improvement in the patients' general condition was a prominent feature. In the successful cases, low-grade fevers disappeared, malaise was less, appetites improved and weight gains were common.

Case A—Disinfection Oleothorax with Reconversion to Pneumothorax

C. D., white male, age twenty-five years. Moderately advanced pulmonary tuberculosis. Left pneumothorax started in December, 1933. One year later, serous fluid formation began and persisted until the spring of 1937, when fluid became purulent. Oleothorax was given in June, 1937 and exudate formation stopped promptly. Because the patient feared a bronchopleural fistula, oil was removed in November, 1938, and an uneventful pneumothorax has been carried on since that time (figure 1). Moderate pleural thickening is present.

This is an example of oleothorax used for the control of tuberculous empyema, followed by reconversion to pneumothorax.

LATE RESULTS AND COMPLICATIONS

Empyema: Of the original group of 36 successful cases, 33 still had a satisfactory oleothorax result at the time of this study. Varying periods of treatment from six months to seven years had elapsed (table 4). The status of these patients and their work capacity are shown. Two

TABLE 4

Late results—work capacity; duration of treatment; empyema group

TIME SINCE INDUCTION OF OLEOTHORAX	DEAD	STILL A PATIENT	NOT ABLE TO WORK	PART-TIME WORK	FULL-TIME WORK	TOTALS
Successful cases						
6–12 months	—	1	6	—	—	7
1–2 years	—	1	2	1	1	5
2–3 years	—	—	—	2	2	4
3–5 years	—	1	—	2	2	5
Over 5 years	—	2	2	3	5	12
Total—successful	0	5	10	8	10	33
Unsuccessful cases						
6–12 months	2	2	1	—	—	5
1–2 years	—	1	2	—	—	3
2–3 years	1	—	—	—	—	1
3–5 years	2	1	—	1	1	5
Over 5 years	—	—	1	—	—	1
Total—unsuccessful	5	4	4	1	1	15

of the 33 cases have been successfully reconverted to pneumothorax; one after eight months, and the other after eighteen months of oleothorax.

The 3 remaining cases who developed late complications are as follows:

1. After four and one-half years of satisfactory oleothorax, this patient developed an extension of tuberculous disease in the opposite lung, and soon after, formed pus under the oil. Oil was aspirated, the disease continued to spread and death followed in six months.

2. After two and one-half years of satisfactory oleothorax, oil was aspirated to permit contralateral collapse therapy. Purulent fluid soon reappeared. Patient died from parenchymal extension after six months.

3. After two years of satisfactory oleothorax, purulent fluid started to form under the oil. Oil was aspirated, fluid formation stopped and patient now has a successful dry pneumothorax, three years later.

While it is gratifying to note the large percentage of long-term, successful cases who have been able to return to active life, some attention should be paid to the 15 cases who were failures or who developed complications.

A careful study of this group reveals that a number of cases were definitely improved by oleothorax and became suitable for other therapy. Only one of the 5 deaths can be in any way connected with oleothorax. This was a case of bronchopleural fistula (case 2), and even this patient lived for two years following the development of the fistula. The other deaths were caused by complications not resulting from the original empyema and oleothorax, and therefore might reasonably have been excluded from the unsuccessful group, as in some cases oleothorax had not had a real trial.

TABLE 5

Results of treatment of simple tuberculous empyema complicating pulmonary tuberculosis

	THORACOPLASTY			OLEOTHORAX		
	Collected cases, Woodruff	Alexander	Hedblom	Authors' series	Collected cases, Woodruff	Collected cases, Howlett
Empyema:						
Cured	7–43.7%	16–76.2%	18–78.2%	33–68.8%	11–50%	80–63%
Living	6–37.5%	1– 4.8%	5–21.8%	10–20.8%	5–22.8%	47–37%
Dead	3–18.8%	4–19.0%		5–10.4%	6–27.2%	
Total	16–100%	21–100%	23–100%	48–100%	22–100%	127–100%

OLEOTHORAX AND THORACOPLASTY IN TREATMENT OF TUBERCULOUS EMPYEMA

In comparing the results of empyema therapy by thoracoplasty (3, 4, 5) and oleothorax (table 5), it is seen that the thoracoplasty "cures" were about as frequent as those with oleothorax. One must remember, however, that selection of cases for thoracoplasty must be far more exclusive than for oleothorax. In other words, the thoracoplasty groups were probably better risks in general than the oleothorax groups. In the present series, many of the patients who were given oil would not have been acceptable for thoracoplasty because of poor general condition or active contralateral disease (35 of 48 cases).

Opposed to this argument in favor of oleothorax, is the fact that successful oleothorax cases risk certain late complications not experienced

by those treated with thoracoplasty. These are bronchopleural and pleurocutaneous fistula and recurrence of empyema.

After considering the various factors involved in selecting the proper procedure, we feel that:

1. All cases of uncomplicated tuberculous empyema should have a period of observation amounting to several months, during which accumulated purulent fluid should be aspirated frequently and other simple therapy applied (irrigations and antiseptics). If improvement is not seen, thoracoplasty and oleothorax should be considered.
2. Cases in whom a permanent collapse is desired and who are good surgical risks, should have thoracoplasty performed.
3. All others should have oleothorax, with thoracoplasty being considered later for patients in whom oleothorax fails.

EARLY RESULTS AND COMPLICATIONS

Obliterative pleurisy: In the group with obliterative pleurisy, 44 of the 53 cases had had gross, serous effusion during the course of the pneumothorax therapy. Nine of these were still forming serous fluid at the time oil was instilled. In 26, the fluid had been purulent at some time and in 14 of these cases, purulent fluid was still being formed at the time oleothorax was induced. In this latter group, however, rapid reëxpansion rather than empyema was considered to be the prime indication for oleothorax. All of the 53 cases had received frequent refills of air at high positive pressures for varying periods of time without success in maintaining the pleural space before oleothorax was recommended. It should be remembered, however, that most cases of premature reëxpansion could be controlled by positive pressures and only the occasional one required oleothorax.

There were a few cases in which pulmonary reëxpansion was so rapid and forceful that oleothorax could not safely be attempted because of the proximity of the lung to the chest wall. A few cases were abandoned after only one or two refills of oil for the same reason. All of these have been omitted from this study.

The criteria of success in this group were the maintenance of an effective collapse of the lung and cessation of fluid formation. Since 24 of the 53 cases were still forming fluid when oleothorax was induced, the latter was an important consideration. As in the empyema group, all cases had been treated with oleothorax for at least six months when the study was made. Success was attained during the first six months

of treatment in 46 of the group of 53 cases and one later success occurred at eighteen months (table 6).

Of the 6 unsuccessful cases, 3 formed purulent fluid persistently:

1. Oleothorax was abandoned after thirty-three months. Pneumothorax therapy resumed; still formed pus; not suitable for thoracoplasty.
2. Formed a small amount of seropurulent fluid under the oil every three to six months. After two and one-half years, fluid became frankly purulent

TABLE 6

Early complications and results; obliterative pleurisy group

FLUID FORMATION AFTER OLEOTHORAX	PREVIOUS CONDITION OF PLEURAL SPACE					
	Always dry	Serous fluid previously	Pus previously	Serous fluid present	Pus present	Total
Successful cases						
No fluid	5	6	8	2	5	26
Serous fluid 1–6 months	1	—	1	5	1	8
Serous fluid 7–18 months	1	1	—	—	—	2
Seropurulent fluid 1–6 months	2	—	—	1	2	5
Purulent fluid 1–6 months	—	1	2	—	2	5
Purulent fluid 7–18 months	—	—	—	—	1	1
Total	9	8	11	8	11	47
Unsuccessful cases						
COMPLICATION						
Persistent pus formation	—	1	—	1	1	3
Bronchopleural fistula	—	—	1	—	1	2
Pleurocutaneous fistula	—	—	—	—	1	1
Total	—	1	1	1	3	6

and oil was discontinued. Pneumothorax was resumed and lung is now being reëxpanded, though a small amount of pus still forms.
3. Fluid formation not decreased in five months. Oleothorax was discontinued and thoracoplasty performed.

Two patients developed bronchopleural fistula:

1. After five months of oleothorax, purulent fluid was still being formed. A small fistula developed, oleothorax was abandoned and lung was reëxpanded. Patient is now well and working.

2. Developed fistula after one month of oleothorax. There was rapid spread of disease in the opposite lung and patient died one week later.

One patient developed a pleurocutaneous fistula:

1. After five months of oleothorax treatment, the fistula developed. Oil was aspirated and the lung was successfully reëxpanded. Recent attempt at follow-up has been unsuccessful. He was working full time when last heard from.

As might be expected, failures and complications were most frequent in those who were forming purulent fluid when the treatment was started. In 5 such cases, however, fluid formation stopped at once after oil was instilled.

Case B—Inhibition and Disinfection Oleothorax

M. M., colored female, age twenty-two years. Far advanced pulmonary tuberculosis with large cavity in right lower half. Right pneumothorax induced in February, 1931, and cavity closure was obtained quite promptly. Serous fluid formation started late in 1931 (figure 2), and became purulent in 1932. Tuberculous empyema was accompanied by a considerable shortening of the existing adhesions and some reëxpansion of the lung (figure 3). Oleothorax was given in August, 1932 (900 cc.). Exudate formation stopped promptly and collapse was maintained. Patient has had refills of oil ranging from 25 cc. to 80 cc. every three months, and has remained well for seven and one-half years (figure 4).

This case is a good example of oleothorax used both for inhibition and control of tuberculous empyema.

LATE RESULTS AND COMPLICATIONS

Obliterative pleurisy: Of the 47 early successes in this group, 5 additional cases had developed complications at the end of the study. The final tabulation (table 7), therefore, shows 42 (79.2 per cent) of the original 53 cases to be successful. The period of treatment and work capacity are shown. The average duration of oleothorax in the successful group was thirty months, and it is interesting to note that there are 7 cases doing full-time work who have had oleothorax for more than five years.

Details of the 5 patients who developed late complications are as follows:

1. Had successful, uncomplicated oleothorax for three and one-half years. Developed a bronchopleural fistula during unusual physical activity when she

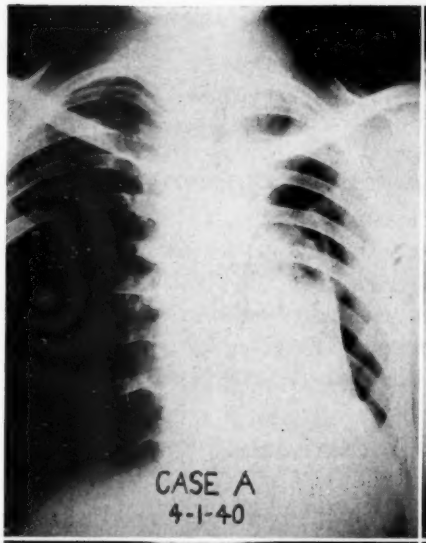


FIG. 1

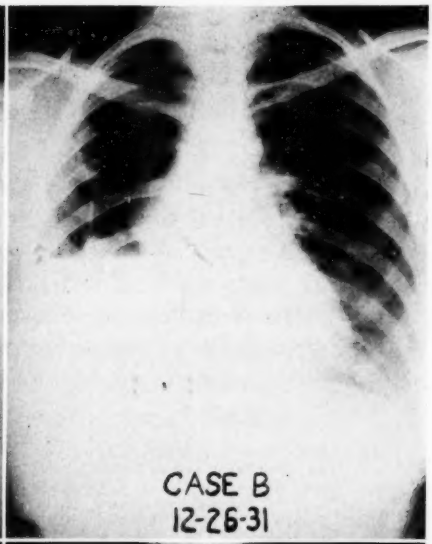


FIG. 2

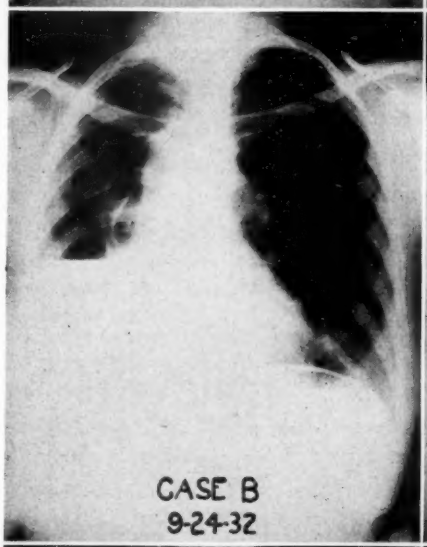
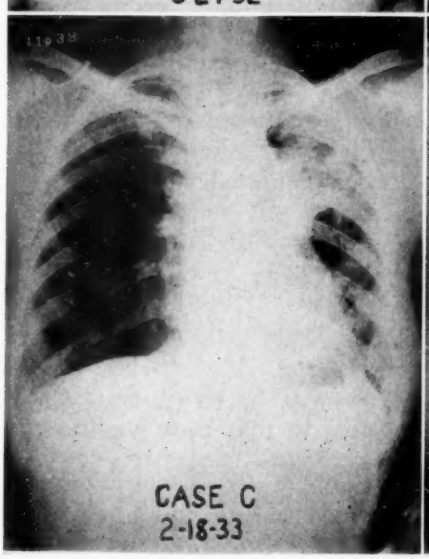


FIG. 3

FIG. 4



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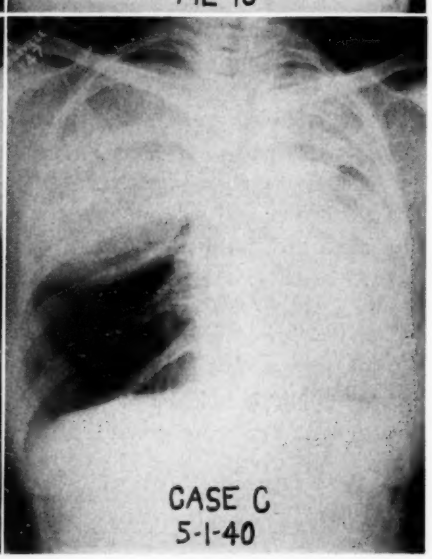

FIG. 6

FIGS. 1–6.

felt something "give way" in her chest. A pneumonic spread appeared in the opposite lung and patient died within two months.

2. After three years of satisfactory oleothorax, pus formed under the oil. Oleothorax was abandoned and an adequate pneumothorax is now maintained. Fluid formation has stopped once more.

3. After seven years of oleothorax, purulent fluid began to form. Oil was removed and pneumothorax reëstablished with pus still being formed.

TABLE 7

Late results—work capacity; duration of treatment; obliterative pleurisy group

TIME SINCE INDUCTION OF OLEOTHORAX	DEAD	STILL A PATIENT	NOT ABLE TO WORK	PART-TIME WORK	FULL-TIME WORK	UN-TRACED	TOTALS
Successful cases							
6–12 months	1	1	7*	4	2	—	15
1–2 years	1	—	2	1	3	—	7
2–3 years	—	2	1	3	1	1	8
3–5 years	—	—	—	1	2	—	3
Over 5 years	—	—	1	1	7	—	9
Total—successful	2	3	11	10	15	1	42
Unsuccessful cases							
6–12 months	1	—	—	—	—	—	1
1–2 years	—	—	—	1	—	—	1
2–3 years	—	—	—	—	2	—	2
3–5 years	1	—	2	—	—	1	4
Over 5 years	—	—	—	3	—	—	3
Total—unsuccessful	2	—	2	4	2	1	11

* Includes 1 case with successful blockade who forms a small amount of pus.

4. After four and one-half years of oleothorax, pus formed under the oil. Oil was removed and the lung reëxpanded. The patient is able to do part-time work.

5. After five and one-half years of oleothorax, patient developed a bronchopleural fistula and a large subcutaneous oil pocket. Oil was aspirated from the chest and the fistula closed. The chest wall collection of oil also disappeared after two aspirations. The patient now has a pneumothorax and forms a small amount of serous fluid.

Analysis of the 11 unsuccessful cases reveals that 2 died following bronchopleural fistula. The other 9 showed no detrimental results, and a number were considerably benefited in that their condition im-

proved or they became suitable for other therapy and eventually recovered.

RESULTS IN PATIENTS WITH FISTULA

Since bronchopleural and pleurocutaneous fistulae are the only important complications, a tabulation of the results of these cases has been made (table 8). It is seen that all of the pleurocutaneous fistulae closed satisfactorily. Three of the 6 bronchopleural fistulae closed, while in the other 3 the fistulae seemed to be at least partially responsible for the patients' deaths.

Secondary infection occurred in only one case. The policy of emptying the pleural pocket promptly when a fistula occurred is probably of importance in the favorable outcome of some of these cases.

TABLE 8

Results in fistula cases

COMPLICATION	EMPYEMA GROUP	OBLITERATIVE PLEURISY GROUP	TOTAL	FISTULA CLOSED	FISTULA CAUSED DEATH	SECONDARY INFECTION
Bronchopleural fistula	2	4	6	3	3	1
Pleurocutaneous fistula	2	1	3	3	0	0

Bronchopleural fistula is a common complication of tuberculous empyema. In Woodruff's collected cases (6), it occurred in 30 per cent of 154 cases. In the present series, 62 patients were forming pus when oleothorax was started. Six of these, about 10 per cent, developed bronchopleural fistulae, and it is difficult to believe that this incidence would have been less had oleothorax not been given. Is it not reasonable to consider bronchopleural fistula a complication of tuberculous empyema rather than of oleothorax?

PROGNOSIS WITH OLEOTHORAX

A further study of the 26 unsuccessful cases in the entire series shows that there is a definite correlation between positive sputum and the results of oleothorax treatment.

Fifteen patients still had a positive sputum when oleothorax was induced. Of this group only 7, or 46.6 per cent, had a successful oleothorax, as contrasted with the group of 86 patients with negative sputum in which there were 67, or 78.8 per cent, successful cases. Howlett (7)

has pointed out that results with oleothorax tend to follow the course of the disease, and we believe that the above statistics confirm that point of view. Additional evidence was seen in 2 cases who had had for some time a successful oleothorax given for empyema. Extension of disease in the opposite lung was followed promptly by reactivation of the empyema with renewed fluid formation on the oleothorax side.

From this we might judge that patients who are doing badly otherwise, or who, because of the extent or distribution of disease, have poor prospects of recovery, are not very likely to be successfully treated with oleothorax.

OLEOTHORAX IN EXTRAPLEURAL PNEUMOTHORAX

Because of fluid formation and contraction of extrapleural pockets, oleothorax has been of real value in maintaining a successful collapse in these patients.

A group of 21 patients has received oleothorax for periods ranging from five to fifteen months with an average of ten and one-half months. Thirteen of the group were forming fluid (serous or purulent) when oleothorax was started. After one month, fluid formation had stopped in all but 4 cases, and at the time of this study, one case only continued to form pus after fourteen months of oil blockade.

Of the 21 cases, 17 are successful and the results are satisfactory. Of the remaining 4, one patient died from other causes, though oleothorax was successful; in another patient the lung reëxpanded, the pocket being lost; the third developed a bronchopleural fistula after one month and is now having a thoracoplasty; the fourth had a persistent cavity because of insufficient collapse and left the hospital without approval after three months of oleothorax.

Case C—Bilateral Oleothorax, Intrapleural and Extrapleural

M. U., white female, age twenty-nine years. Far advanced pulmonary tuberculosis. Patient admitted in February, 1933. The most prominent disease was in the left upper half; however, there was bilateral upper lobe ulceration (figure 5). Left pneumothorax was started in February, 1933 and incomplete collapse was obtained. Serous fluid formation with some reëxpansion occurred in June, 1933. As even the limited collapse obtained was apparently successful in closing the cavities present, a left inhibition oleothorax was given in June, 1933. Right pneumothorax was started in November, 1933, and a satisfactory selective collapse of the right upper lobe obtained with cavity closure after a few months. The patient followed a satisfactory course with negative sputum for a period of five and one-half years, or until May, 1939,

when the right lung reëxpanded as a result of obliterative pleurisy. Two months later, in July, 1939, an acute spread of disease in the right upper lobe appeared with a cavity measuring about 3 cm. in diameter. Pneumothorax was attempted on the right again and failed. An extrapleural pneumothorax was performed on the right in September, 1939, and resulted in cavity closure and negative sputum. To maintain the extrapleural pocket, a right extrapleural oleothorax was given in January, 1940. In the meantime, no additional oil is being given on the left, with the hope that through oil absorption the patient's vital capacity will be increased. On May 1, 1940, sputum was negative, and vital capacity was 38 per cent (figure 6).

DISCUSSION

A number of interesting problems connected with this study have arisen:

1. How long should oleothorax be continued? This will doubtless vary with the individual case, the extent of disease and the original indications. We have been in no hurry to discontinue this therapy in view of the low percentage of complications. Pneumothorax has been cautiously reëstablished in place of oleothorax in a few cases when we felt the purpose of the oil had been safely accomplished. While our experience in this matter is limited, we feel that this can be done rather frequently in inhibition oleothorax, but that there is some danger of renewed fluid formation in patients who have had empyema. Further attempts to substitute air for oil should be made, though many patients are reluctant to have any change made in an uneventful oleothorax. Such a policy might diminish the danger of late complications.

2. What are the prospects for reëxpanding a lung, long collapsed by oleothorax? On this point we cannot speak with much authority. Four of the 5 reëxpanded lungs in our series had not had oleothorax more than nine months, and in this group reëxpansion was not difficult. We see no reason to believe that the pleura will be thicker or reëxpansion more difficult after oleothorax than after empyema alone. Whether or not the pleura will be seriously thickened by oleothorax in patients with dry obliterative pleurisy remains to be seen. We realize that complete reëxpansion will be impossible in a certain number of these cases, because of either parenchymal or pleural fibrosis, and that thoracoplasty may eventually be performed in some because of complications. The time of operation, however, will be elective and many patients will be able to withstand the procedure who could not have done so at the time of induction of oleothorax.

3. How does oleothorax therapy affect pleural fluid formation? Is the

effect mechanical or chemical? Is the mildly antiseptic gomenol of any importance? Our only comments with regard to these questions are based on observations made from time to time. An occasional case of persistent empyema shows a sudden cessation of fluid formation after only one or two instillations of oil, suggesting a chemical or antiseptic effect. Additional evidence is the marked decrease in the number of organisms in the pleural exudate after only one instillation of oil. Two or three pleural exudates which contained large numbers of bacilli on the day oleothorax was started became negative on smear examination when the fluid was withdrawn at the time of the second treatment, two or three days later. On the other hand, we have frequently noticed patients with simple tuberculous empyema who showed little or no response to a 60 or 70 per cent oleothorax carried for several months, but promptly stopped forming fluid when the chest was completely

TABLE 9

Summary of successful cases

INDICATION	TOTAL CASES	EARLY SUCCESSES	CONTINUED SUCCESSFUL
Tuberculous empyema	48	36–75%	33–68+%
Obliterative pleurisy	53	47–88%	42–79+%

filled with oil. This suggests some mechanical effect from the complete blockade. Another explanation of the effectiveness of a complete oleothorax in empyema might be the loss of oxygen supply for the aerobic tubercle bacillus, when the air is completely removed (8). A number of other hypotheses have been advanced to explain the mechanism of action. These include the development of a proteolytic ferment in the chest cavity in the presence of oleogomenol and also the development of a lipolytic effect on the capsule of the tubercle bacillus.

SUMMARY

A series of 101 cases of oleothorax is presented with indications, complications and results in treating tuberculous empyema and obliterative pleurisy (table 9). An additional series of 21 cases of oleothorax used in connection with extrapleural pneumothorax is presented briefly. Several questions and unsolved problems are discussed.

CONCLUSIONS

We are conscious of the fact that oleothorax results have been unsatisfactory in many clinics. With a better understanding of technique and

the proper selection of cases, however, results will be improved, and oleothorax should assume its limited but valuable place in the treatment of tuberculosis.

The following conclusions seem to us to be justified:

1. Oleothorax is an indispensable procedure when used to inhibit premature reëxpansion of lungs collapsed by pneumothorax. For this purpose it is successful in about 80 per cent of cases.

2. Simple tuberculous empyema responds frequently to such methods as aspiration, irrigation and medications. When empyema persists, oleothorax is the procedure of choice in most cases and successful results will be attained in about 70 per cent of the patients.

3. Oleothorax may be considered as a temporary stop-gap or substitute for thoracoplasty in the treatment of some patients with empyema; however, in view of the duration of this therapy in many cases, oleothorax ranks as a form of permanent therapy for most of those patients in whom fluid formation is inhibited.

4. During a brief experience oleothorax has been valuable in maintaining and controlling extrapleural pneumothorax spaces.

5. Further experience in the results attained both in reconversion to pneumothorax and reëxpansion will be of great aid in evaluating the permanent benefits of oleothorax.

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RESPIRATORY RESERVE BEFORE AND AFTER THORACOPLASTY[1,2]

G. F. PILTZ, T. DE CECIO, W. CHAPMAN AND B. P. POTTER

With the increasing use of collapse therapy in the treatment of tuberculosis, the study of respiratory reserve has assumed greater importance in recent years. In the majority of these patients the reserve is more than adequate to meet their usual needs, but when surgical alterations of the thoracic cage are imposed upon those whose reserve is already diminished, dyspnoea is apt to occur postoperatively. Although this dyspnoea is often transient, in some patients its persists and results in the curtailment of physical activity. The dyspnoea which occurs in these patients both preoperatively and postoperatively, excluding that due to circulatory disease, is a function of the changes in the mechanics of respiration. By measuring vital capacity an index of the degree of these alterations can be obtained. But such measurements alone are inadequate since they are spatial and do not consider the temporal factor or conditions of stress. During periods of stress the tidal air is related to the rate of respiration and the volume must be measured at this particular respiratory rate. A comparison of the tidal air at rest and immediately after a period of exercise should fulfill this conception of pulmonary reserve.

Our procedure consisted of comparing tidal air with the maximal tidal air obtained immediately after the cessation of an exercise period. The tidal air was obtained from a record of the patient's breathing under basal conditions, employing a Benedict-Roth basal metabolism machine. The exercise consisted of the step-test of Master (1) from whose tables a standard amount of exercise depending upon the patient's weight and age was obtained. Immediately upon conclusion of the exercise, the patient was connected with the basal metabolism machine and a record obtained. Usually about twenty seconds elapsed between the end of the exercise and the beginning of the record. In all cases the greatest

[1] Read before the American Academy of Tuberculosis Physicians, New York City, June 11, 1940.

[2] From the Hudson County Tuberculosis Hospital, Jersey City, New Jersey.

inspiratory response was used and this was called the tidal air after exercise. In addition the respiratory rates were calculated from the tracings. All of the patients who were subjected to these step-tests were accustomed to moderate exercise. The step-test as a method of exercise is useful since the amount of work done is measured and hence can be exactly repeated in subsequent tests on the same patient.

The normals: Readings on 18 members of the hospital staff were done. The results are shown in table 1. The age group was similar to that of

TABLE 1

Observations on a group who have no pulmonary disease

NAME	TIDAL AIR AT REST	TIDAL AIR AFTER EXERCISE	RATE OF RESPIRATION		PERCENTAGE INCREASE AFTER EXERCISE
			Rest	Exercise	
T. D.	603	1,520	15	14	150
G. P.	699	1,503	7	7	110
W. C.	506	1,355	8	9	160
T. V.	459	1,148	11	19	150
B. E.	447	1,180	12	17	160
A. P.	617	1,938	10	10	210
A. C.	524	1,746	13	11	230
B. G.	570	1,491	11	12	160
A. C.	658	1,754	13	13	160
M. L.	430	943	14	20	120
M. M.	404	1,147	16	15	180
G. K.	558	1,288	12	12	130
T. L.	472	983	9	15	100
J. W.	454	1,110	10	17	140
I. L.	372	1,248	16	14	230
H. C.	470	1,025	15	18	110
A. B.	295	855	20	22	190
H. K.	429	1,251	15	18	190

the patients. The average increase of the tidal air after exercise over the tidal air at rest was 160 per cent. The minimum value was an increase of 100 per cent and the maximum 230 per cent.

The tidal air after exercise was at least twice the tidal air in all cases in this group. There was but little increase in the respiratory rate after exercise; in about one-half of the cases the rate was the same immediately after exercise.

Patients before and after thoracoplasty: Nineteen patients are represented in this group and the last measurements were made about six months after the final stage. These results are presented in table 2.

TABLE 2

Before and after thoracoplasty

PATIENT	TIDAL AIR AT REST	TIDAL AIR AFTER EXERCISE	RATE OF RESPIRATION		PERCENTAGE INCREASE AFTER EXERCISE	REMARKS*
			Rest	Exercise		
M. L.	284	738	26	29	160	
	298	718	24	33	140	
H. T.	468	603	15	27	28	Dyspnoea on exertion
	350	463	17	38	32	Dyspnoea on slight exertion
M. K.	325	823	17	19	150	
	327	727	16	17	120	
M. G.	280	1,113	13	19	330	
	394	979	14	19	150	
M. C.	488	698	13	28	43	Dyspnoea on exertion
	456	564	15	37	23	Dyspnoea on slight exertion
W. M.	660	1,606	12	18	140	
	647	1,486	12	19	130	
F. M.	494	808	16	25	63	
	350	590	16	32	66	Slight dyspnoea
G. B.	386	936	15	18	140	
	522	988	9	15	89	
A. T.	517	1,451	19	20	180	
	469	1,351	10	14	180	
T. McK.	445	988	13	21	120	
	432	963	12	15	120	
F. D.	644	1,377	8	14	110	
	606	1,346	9	14	120	
L. B.	465	831	14	25	78	
	512	629	15	34	22	Dyspnoea on exertion
E. H.	418	1,077	26	31	160	
	255	859	26	25	230	
M. M.	381	1,258	12	13	230	
	294	629	13	20	110	

The first figure in each column for each patient is the preoperative; the second figure is the postoperative finding.

* Unless special remarks are included, no dyspnoea occurred.

TABLE 2—*Concluded*

PATIENT	TIDAL AIR AT REST	TIDAL AIR AFTER EXERCISE	RATE OF RESPIRATION		PERCENTAGE INCREASE* AFTER EXERCISE	REMARKS
			Rest	Exercise		
A. K.	523	1,240	8	12	130	
	485	1,038	9	14	110	
A. L.	238	639	18	23	170	
	275	532	14	26	97	
H. Z.	443	1,078	15	17	140	
	389	1,151	13	19	190	
R. R.	593	1,254	13	17	110	
	469	865	13	26	84	
V. W.	362	833	21	33	130	
	335	731	25	33	120	

TABLE 3

Patients who have had thoracoplasty from three to eight years previously

NAME	TIDAL AIR AT REST	TIDAL AIR AFTER EXERCISE	RATE OF RESPIRATION		PERCENTAGE INCREASE	REMARKS*
			Rest	Exercise		
A. N.	784	983	8	18	25	Dyspnoeic on slight exertion
E. A.	342	600	15	24	75	Dyspnoeic on 2 flights
L. M.	457	700	26	30	53	Dyspnoeic on 1 flight
H. B.	434	730	17	26	68	Dyspnoeic on 1 flight
A. G.	394	790	10	18	100	
A. N.	335	720	17	21	110	
N. D.	308	1,090	25	27	250	
M. S.	395	800	17	27	100	
E. S.	275	740	21	27	170	
H. G.	271	600	22	32	120	
R. S.	252	579	16	20	130	
K. M.	353	918	15	19	160	
A. H.	311	624	11	18	100	
J. C.	494	1,170	10	11	130	
H. D.	355	846	18	21	130	
A. Z.	388	610	14	32	57	Could do 1 flight slowly without dyspnoea
R. R.	201	538	18	31	160	
A. M.	391	937	14	16	140	
E. E.	288	716	18	23	150	
L. M.	314	519	18	30	65	Dyspnoea on slight exertion

* Unless special remarks are included, no dyspnoea occurred.

The average increase before thoracoplasty was 137 per cent and after thoracoplasty 112 per cent; the minimum value before operation was 28 per cent and after operation 22 per cent; the maximum value before operation was 330 per cent and 230 per cent after operation.

In this group there were two patients (H. T. and M. C.) whose tidal air after exercise increased less than 50 per cent. Before operation both of these patients were slightly dyspnoeic after slight exertion and showed marked increases in respiratory rate after exercise. The dyspnoea was even more pronounced after operation. A third patient (F. M.) showed slight dyspnoea both before and after operation and in this case the increase of tidal air after exercise was low with a corresponding increase in respiratory rate. A fourth patient (L. B.) showed no unusual distress before operation but afterwards was definitely dyspnoeic on exertion and in this instance a marked fall in the tidal air after exercise was found, with a corresponding increase in respiratory rate.

Patients in whom thoracoplasty was done from three to eight years ago: No measurements before thoracoplasty are available in this group of 20 patients. The results are shown in table 3. The average increase was 114 per cent with a minimum of 25 per cent and a maximum of 250 per cent. In this group it was again noted that the greatest amount of dyspnoea occurred in those whose values were only 50 per cent or less and in these the respiratory rates were the highest after exercise.

DISCUSSION

Cournand and Richards (2) state that the maximum ventilation per minute, or maximum breathing capacity, adds to lung volumes the dimension of time and estimates the availability of the spatial vital capacity for gross air circulation. Similarly the tidal air after exercise is related to time. The amount that the chest expands or contracts is related not only to its ability to expand or contract, but also to the time in which it has to do it. It is significant that those patients whose tidal air after exercise increased 50 per cent or less were also the patients who had the greatest increases in respiratory rates after exercise. The mechanism is probably similar to that in chronic emphysema, where the position of the chest is nearly in full inspiration and the residual air increased, while the complemental air is reduced. Lambert, Berry, Cournand and Richards (3) observed that in emphysema, maximum voluntary ventilation is performed by great increase in respiratory rate, with small amplitude per breath. However, the changes which we have

noted cannot be explained by emphysema alone. Since the patients who have been operated for three or more years have volume increases comparable to the normals, it is evident that there have not occurred any extensive changes in lung volumes comparable to chronic emphysema. Of greatest importance is the fact that by this method an index of respiratory reserve is easily obtained and that it is applicable to the ordinary ambulant patient. It is significant that the method is dependent upon involuntary responses, thus eliminating the necessity for training and minimizing psychic influences.

SUMMARY

1. The percentage increase of the tidal air after exercise over the tidal air at rest is compared in a group of normals, in a group before and about six months after thoracoplasty and in a group from three to eight years after thoracoplasty.

2. In the normal group, the tidal air after exercise is at least 100 per cent greater than the tidal air before exercise.

3. The patients whose tidal air after exercise increases but 50 per cent or less also show the greatest increase in respiratory rate and exhibit dyspnoea. These individuals are classified as having a poor respiratory reserve.

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TUBERCULOSIS IN THE JEWISH DIABETIC[1, 2]

ARTHUR REST

The association of pulmonary tuberculosis with other nontuberculous conditions influences to a great extent the course of the tuberculous infection. The pulmonary lesion may be relatively benign, but its conversion to a fulminating type may become apparent after the development of another disease. Diabetes mellitus alters the metabolic equilibrium of the organism and may predispose to a subsequent infection, of which, some believe, pulmonary tuberculosis may be the secondary intercurrent disease. On the other hand, pulmonary tuberculosis may have preceded the diabetes. In that case, the course of the pulmonary lesion may be altered and complicated by the latter.

The mortality of tuberculosis of the Jews is definitely lower than that of other people. Bolduan and Weiner (1) state that in tuberculosis the Jewish people show a considerably lower mortality rate than do non-Jews, the difference being especially marked among the males. Thus, between the ages of thirty and fifty the proportion of tuberculosis deaths among Jewish males was approximately one-third of that among non-Jewish males. With a few exceptions, the disease assumes the characteristics of the fibroid type of the "good chronic," exhibiting the manifestations of high immunity. Diabetes is common in the Jewish people (2) and in New York City alone, the source of most of our patients, this disease is some 75 per cent more prevalent than among non-Jews. In Joslin's clinic (3) 13 per cent of the diabetic patients studied are of Jewish origin. The New York Bulletin (1) states that in both males and females at almost all age periods, diabetes causes more deaths among the Jewish people than others. Among the Jewish females, the proportion is about double that in non-Jews. Diabetes is believed to result in a pulmonary lesion of a highly allergic nature. It is my endeavor to present particularly the effects of diabetes upon the supposedly "good chronic," the Jewish tuberculous patient.

[1] From the Medical Department of The Sanatorium of the Jewish Consumptives' Relief Society, Spivak, Colorado.

[2] Presented at the regular meeting of the Denver Sanatorium Association, Spivak, Colorado, October 24, 1939.

In the Baker Clinic Bulletin (4) it is pointed out that the morbidity and mortality of diabetes have increased substantially in the last five years. Tuberculosis, on the other hand, has taken a downward trend. It is the general opinion, shared by Joslin (5), that diabetes predisposes to pulmonary tuberculosis. We who spend a great part of our medical career doing institutional work, are aware of the relative infrequency of diabetes and pulmonary tuberculosis. If diabetes is on the increase and makes the individual more susceptible to pulmonary tuberculosis (which is still a problem) it is logical to ask why the incidence of the combination is not higher. Montgomery (6) discovered .15 per cent of diabetics in 31,834 tuberculous patients. Banyai (7) found .59 per cent in 5,224 tuberculous patients. The National Jewish Hospital (8) reports that there were 25 diabetic tuberculous Jewish patients in that institution from January 1, 1928 to December 31, 1938. The Sanatorium of the Jewish Consumptive Relief Association at Duarte, California (9) mentions that there were 17 diabetics in that institution in the past ten years. Weiner and Kavee (10) studied 218 diabetic cases or 6.4 per cent of 3,385 Jewish patients admitted to the Montefiore Hospital over a ten-year period ending December 31, 1932. This is a percentage higher than has been reported by others, for the reason that many hospitals and clinics in New York City send these cases to that institution for treatment. In addition to the number of Gentile admissions (whose cases are not included in this study) there were 1,360 Jewish patients admitted to our institution for the first time from February 1, 1927 to August 1, 1939. Of these 34, or .025 per cent, had diabetes and tuberculosis of whom 23, or 67.7 per cent, were males and 11, or 32.3 per cent were females. There were 7, or 20 per cent, with diabetes in the family and 11, or 32.3 per cent, with tuberculosis in the family.

Table 1 shows the relation of onset of pulmonary tuberculosis and diabetes and the time interval of their occurrence. According to Root (3) the combination is seen more frequently than before the insulin era for the reason that diabetics live longer and have a greater opportunity to contract the disease. This is substantiated in table 2, as concerns admissions to this Sanatorium.

Fett (11) states that most cases of diabetes and tuberculosis occur after the age of forty. The age groups of my 34 cases are illustrated in table 3.

The length of time that these patients have had their diabetes, tuberculosis and a combination of the two is of interest (table 4).

Diabetes occurring after the development of pulmonary tuberculosis is unusual. Fishberg (12) dealt with thousands of Jewish tuberculous patients. Very few developed glycosuria while suffering from active

TABLE 1

CASES OF	TOTALS	LESS THAN 1 YEAR	1 TO 2 YEARS	2 TO 3 YEARS	3 TO 5 YEARS	5 TO 7 YEARS	7 TO 10 YEARS	10 TO 15 YEARS	15 TO 20 YEARS
Diabetes preceding tuberculosis:									
Number	26	3	10	2	4	1	2	3	1
Per cent	76.5	11.6	38.4	7.7	15.4	3.8	7.7	11.6	3.8
Tuberculosis preceding diabetes:									
Number	6	1	2	0	1	1	0	0	1
Per cent	17.6	16.7	33.3	0	16.7	16.7	0	0	16.7
Diabetes diagnosed with tuberculosis:									
Number	2								
Per cent	5.9								

TABLE 2

YEAR ADMITTED	YEARLY NUMBER JEWISH FIRST ADMISSIONS TOTAL 1,360	YEARLY NUMBER OF DIABETICS WITH TUBERCULOSIS	YEARLY PERCENTAGE OF DIABETIC TUBERCULOUS
February 1, 1927	135	2	0.015
1928	184	4	0.022
1929	127	2	0.016
1930	136	0	0
1931	94	2	0.021
1932	69	0	0
1933	74	0	0
1934	90	2	0.022
1935	94	3	0.032
1936	122	3	0.025
1937	82	5	0.061
1938	86	5	0.058
August 1, 1939	65	6	0.092

pulmonary tuberculosis. Montgomery (6) failed to find a single authentic case of diabetes occurring in a patient with an active lesion. In a total of 701 diabetic patients admitted to Montefiore Hospital (10) 5 or .7 per cent developed pulmonary tuberculosis while under observation at that institution. Six cases were encountered in this Sanatorium.

The question may arise, if diabetes predisposes to pulmonary tuber-

TABLE 3

Diabetes occurred in two age groups, the large majority between the ages of fifteen and forty-five and a small number between fifty and fifty-five. Tuberculosis became manifest in two distinct age groups, twenty to thirty and forty to fifty-five. The greatest number of deaths occurred between the ages of forty and sixty

AGES	ONSET OF DIABETES		ONSET OF TUBERCULOSIS		AGE AT DEATH, DIABETES AND TUBERCULOSIS	
	Number	Per cent	Number	Per cent	Number	Per cent
years						
10–15	2	5.9				
15–20	4	11.8	2	5.9	1	7.7
20–25	5	14.7	6	17.6		
25–30	3	8.8	7	20.6		
30–35	4	11.8	2	5.9	1	7.7
35–40	6	17.6	2	5.9	1	7.7
40–45	3	8.8	3	8.8	4	30.7
45–50	2	5.9	6	17.6	2	15.4
50–55	4	11.8	4	11.8	2	15.4
55–60	1	2.9	2	5.9	2	15.4
Totals....	34	100.0	34	100.0	13	100.0

TABLE 4

In the living patients, the majority have had diabetes for from one to fourteen years and tuberculosis for from one to twelve years, and the combination for from one to eight years. In the dead patients, diabetes was present for from one to four years, tuberculosis for from one to two years and the combination for from less than one to two years

DURATION OF	LIVING	DEAD	LESS THAN 1 YEAR	1 TO 2 YEARS	2 TO 4 YEARS	4 TO 8 YEARS	8 TO 12 YEARS	12 TO 14 YEARS	14 TO 18 YEARS	18 TO 23 YEARS
Diabetes to August 1, 1939:										
Number	21		0	3	4	5	3	4	1	1
Per cent			0.0	14.3	19.0	23.8	14.3	19.0	4.8	4.8
Diabetes to death:										
Number		13	0	6	3	1	1	1	1	0
Per cent			0.0	46.1	23.1	7.7	7.7	7.7	7.7	0.0
Tuberculosis to August 1, 1939:										
Number	21		1	4	4	6	4	1	0	1
Per cent			4.8	19.0	19.0	28.6	19.0	4.8	0.0	4.8
Tuberculosis to death:										
Number		13	1	10	1	1	0	0	0	0
Per cent			7.7	76.9	7.7	7.7	0.0	0.0	0.0	0.0
Tuberculosis and diabetes to August 1, 1939:										
Number	21		1	5	3	7	2	0	1	2
Per cent			4.8	23.8	14.3	33.3	9.5	0.0	4.8	9.5
Tuberculosis and diabetes to death:										
Number		13	3	7	1	0	0	1	1	0
Per cent			23.1	53.8	7.7	0.0	0.0	7.7	7.7	0.0

culosis, what changes are produced in the individual to promote this susceptibility? According to Long (13) who feels that diabetes predisposes to tuberculosis, there is no explanation based on proven facts. In a personal communication he states that the addition of glucose to ordinary artificial culture media seems to enhance the growth of the tubercle bacillus. By analogy, he thinks that the hyperglycaemia of the diabetic would aid in the growth of the tubercle bacillus in the body. Secondly, there is a much disturbed fat metabolism in diabetes, probably with an excessive concentration of the products of incomplete destruction of fats. He cannot avoid the impression that there must be an excess of glycerol in the body fluids as a result of this breakdown of fats. Glycerol is one of our best food materials for the growth of the tubercle bacillus. If this product does occur in excess quantities in the body fluids of diabetics, improved growth might be expected on that score. In addition, the altered metabolism in the diabetic produces acidosis by virtue of the formation of ketone bodies, and this may be aided by the elimination of nitrogen from tissue breakdown. Smithburn (14) has shown in experimental work that the virulence of the tubercle bacillus can be altered at will by changing the reaction of the media, that is, the more acid the media, the more virulent is the organism. Keeton (15), another adherent to the belief that diabetes predisposes to tuberculosis, in a personal communication, states that the appearance of an acidosis destroys the resistance of the tissues, and favors the spread of a tuberculous process. He is not so convinced that a hyperglycaemia alone is responsible for this lack of resistance. Muller (16) believes that in hyperglycaemia the blood is less bactericidal than normal blood. The same is true for the serum in other diseases leading to cachexia without hyperglycaemia. He therefore concurs with Keeton that it is not only the hyperglycaemia, but in addition a disturbed function of the leucocytes and tissues in general, furnishing better conditions for the growth of bacteria. It is my opinion that if the altered metabolism enhances the growth of the tubercle bacillus, it may have the same effect on other organisms in the bronchial tree. The increased virulence of the mixed infection may particularly contribute to the unfavorable course of the diabetic.

Assuming that diabetes does predispose to pulmonary tuberculosis, one might expect to see more tuberculous juvenile diabetics. Of the 34 cases studied by me, two developed tuberculosis at an age where they could be considered in this category. Positive tuberculin reactors

in children are not as common as heretofore. Chadwick (17) concludes that of each 100 children in the general population between the ages of five and fifteen years, 28 per cent react to tuberculin. Only 1 per cent show X-ray changes requiring continued medical attention. According to Root (3) 37 per cent of the juvenile diabetics in Boston and also in Vienna in 1937 had positive Mantoux tests. Joslin (5) reports 6 cases of tuberculosis among his 147 juvenile diabetics and a mortality of 40 per cent, due to tuberculosis in diabetic children at ages from ten to fifteen years (18). Long (13) feels that diabetes early in the course of the primary infection could prevent healing and lead to progressive pulmonary tuberculosis. Keeton (15) mentions that according to statistics the incidence of diabetes occurs in later life. Hence, more individuals have passed the period where they have had the primary complex. He cites the case of a boy eight years of age who developed a primary complex after he had had diabetes for some four years. With the use of protamine zinc insulin and an adequate control of the diet, he had been managed successfully. In the process of treatment, his mother, against instructions, exposed the boy to sunlight. A check-up plate made some four weeks after he had had daily exposures showed a marked increase in the reaction about the complex. This promptly regressed with bed-rest and withdrawal of the boy from sunlight. The limited comparative statements have shown that the percentage of positive tuberculin reactors in diabetic children is higher, the incidence of tuberculosis is greater and the mortality is increased over that of nondiabetic children. The evidence is such that in diabetic juveniles there may be a greater susceptibility to tuberculosis.

The lesion most commonly seen in the Jewish tuberculous patient is conspicuous by its expression of high immunity in a people in whom tuberculosis has existed for many centuries. The marked fibrosis, with or without cavitation, is in contrast to the acute, rapidly progressive, exudative and caseous pneumonic lesion of the primitive races. Sosman and Steidl (19) found that 46 per cent of the diabetics studied had hilar lesions, the apices being spared. Some go so far as to state that the hilar, pneumonic lesion is typical of the diabetic tuberculous. This distribution occurred very rarely in our series, but it was noted that lesions near the hilum were more frequently included in the extensive pulmonary involvement than in the nondiabetic tuberculous patient. No part of the lung, however, was spared in the diabetic.

In my series of 21 living, diabetic, tuberculous patients, only one, or

5 per cent, had a moderately advanced lesion, which was of the biapical infiltrative type. The diabetes was of moderate severity. The other 20, or 95 per cent, were far advanced. Nine patients, or 43 per cent, had extensive lesions of both lungs; 7, or 33 per cent, had the major lesion in the left lung; 3, or 14 per cent, had the predominant lesion in the right lung, and one, or 5 per cent, had a similar infiltrative lesion of both lungs. The lesions were chiefly fibro-ulcerative and had extensive soft shadows throughout the parenchyma. The entire group was sputum-positive on admission. The 3 who became negative did so following some form of collapse therapy. Not one case had the X-ray characteristics of a haematogenous spread. The only complications were in 3 patients who had tuberculous laryngitis; not a single case of tuberculous enteritis was diagnosed. Muller (16) commented on this same observation and attempted to explain it on the high vitamin content of the diabetic diet. The diabetes of the patients reviewed ranged from mild to severe. Three gave a history of coma.

The 13 patients who died had lesions similar to those of the living. All were in the far advanced stages of the disease. Nine, or 69 per cent, had extensive involvement of both lungs; 3, or 23 per cent, had the major lesion in the right lung and 1, or 8 per cent, had the greater involvement in the left lung. The lesions were so extensive as to prevent any form of successful collapse therapy. Their sputa were always positive. Two had tuberculous laryngitis and one had tuberculosis of the tongue. The diabetes ranged from moderate to severe. It is noteworthy that 4 died of haemoptyses and the remaining 9 of asthenia. Tuberculous patients usually die of some pulmonary or extrapulmonary complication. The fact that the large percentage died of asthenia suggests the possibility that diabetes was a contending contributory factor.

In the 6 cases where tuberculosis preceded diabetes, the pulmonary lesion was milder and more easily controlled. One died and the remaining 5 are living; 2 of them are working and the other 3 are curing.

It is interesting to analyze these 34 patients as regards their tuberculosis and not to consider their diabetes. The majority represent that category of tuberculous patients seen in every institution and for whom no form of therapy can be instituted. There is nothing in the lesion that would make one suspect that diabetes coexisted. Of the 34 cases, only one with the moderately advanced lesion went on to spontaneous quiescence. Wessler and Hennel (20), on the other hand, report 8 tuberculous diabetics with cavities who proceeded to closure with no

form of collapse therapy, and 3 cases of pneumonic infiltration that rapidly regressed. They feel that the lesion in the diabetic may be as benign as that in the nondiabetic. Keeton (15) assumes an opposite view and states that the diabetic is more apt to have an exudative reaction, and rarely reaches the stage at which proliferation occurs. Wessler and Hennel (20) conclude that tuberculosis in diabetics is not inherently or necessarily progressive or fatal.

The problem of early recognition of tuberculosis is essential if one is to manage properly the diabetic tuberculous. The diabetic who, although adequately controlled, does not improve correspondingly, the one with unexplained catarrhal symptoms, or the patient with a prolonged upper respiratory infection, should be X-rayed. With proper collapse therapy, the major problem confines itself to management of the diabetes. Once the lesion becomes advanced and collapse therapy is not possible the picture changes. The active therapy is directed towards controlling the diabetes in the presence of a progressive pulmonary lesion, in the hope that the body forces will arrest the disease. This favorable course occurred but rarely in our series.

The longevity of the diabetic tuberculous unamenable to collapse therapy is far from encouraging. According to Fett (11) when open tuberculosis is associated with diabetes, the average expectancy of life is under three years and is barely half of what it would be in the case of open tuberculosis uncomplicated by diabetes. Fitz (21) reported that 86 per cent of his cases died in a seven-year period. Root (3) states that 69 per cent of his fatal cases treated with insulin lived 8.6 years. Of the 17 diabetic tuberculous cases admitted over a ten-year period to the Sanatorium of the Jewish Consumptive Relief Association (9) at Duarte, California, 11 are dead, 3 left in fair condition and are untraceable and 3 are curing. Of Weiner and Kavee's (10) 218 patients, 68 per cent died within two years.

SUMMARY

Thirty-four, or 0.025 per cent, of 1,360 patients admitted from February 1, 1927 to August 1, 1939 had diabetes and tuberculosis.

21 or 61 per cent are still living over a ten-year period.
13 or 38 per cent are dead over a twelve-year period.

26 or 77 per cent of the 34 cases developed diabetes first.
6 or 18 per cent of the 34 cases developed tuberculosis first.
2 or 6 per cent had diabetes diagnosed with tuberculosis.

19 or 73 per cent had diabetes for from less than one year to five years before the onset of tuberculosis.
5 or 19 per cent had diabetes for from seven to fifteen years before the onset of tuberculosis.

Of the 6 cases where tuberculosis preceded diabetes:
3 or 50 per cent had tuberculosis for from less than one year to two years.
2 or 33 per cent had tuberculosis for from three to seven years.

AGES

25 or 74 per cent developed diabetes between the ages of fourteen and forty-five.
4 or 12 per cent developed diabetes between the ages of fifty and fifty-five.

13 or 38 per cent developed tuberculosis between the ages of twenty and thirty.
13 or 38 per cent developed tuberculosis between the ages of forty and fifty-five.

LIVING

19 or 91 per cent of those living have had diabetes for from one to fourteen years.
18 or 87 per cent of those living have had tuberculosis for from one to twelve years.
15 or 72 per cent of those living with diabetes and tuberculosis have had the combination for from one to eight years.

DEAD PATIENTS

9 or 69 per cent had diabetes for from one to four years.
10 or 77 per cent had tuberculosis for from one to two years.
10 or 77 per cent had diabetes and tuberculosis from less than one to two years.
10 or 77 per cent with diabetes and tuberculosis died between the ages of forty and sixty years.

LIVING PATIENTS

21 Cases:
20 or 95 per cent were far advanced.
1 or 5 per cent was moderately advanced.

Type of Lesion:
9 or 43 per cent had extensive involvement of both lungs.
7 or 33 per cent had the major lesion in the left lung.
3 or 14 per cent had the major lesion in the right lung.
1 or 5 per cent had an extensive infiltrative lesion of both lungs.
1 or 5 per cent had a moderately advanced lesion of both upper lobes.

Sputum:
21 or 100 per cent were positive on admission.
3 or 14 per cent were negative on discharge and include the collapse therapy cases.

Treatment of Tuberculosis and Results:
6 or 29 per cent had bed-rest only. Of this number 4 are still curing; one is quiescent and working; one is arrested and working.
6 or 29 per cent had left artificial pneumothorax. One is improved and working; 5 are curing.

1 had a three-stage thoracoplasty and is arrested and working.
5 had bilateral pneumothorax and are curing.
2 had right artificial pneumothorax and are curing.
1 had a left phrenic crush and is curing.

Average Blood Sugar:
10 or 48 per cent had 160 mg.
8 or 38 per cent had 250 mg.
3 or 14 per cent had 350 mg.

Treatment of Diabetes:
14 or 67 per cent received protamine zinc insulin.
4 or 19 per cent received protamine zinc insulin and insulin.
3 or 14 per cent received plain insulin.

Complications:
14 or 67 per cent had no complications.
3 or 14 per cent had tuberculous laryngitis.
3 or 14 per cent had history of coma.
1 or 5 per cent had diabetic retinitis.

Present Condition:
17 or 81 per cent are curing.
4 or 19 per cent are working.

PATIENTS WHO DIED

Type of Lesion:
13 or 100 per cent had far advanced lesions.

Involvement:
9 or 69 per cent had extensive involvement of both lungs.
3 or 23 per cent had extensive involvement of the right lung, particularly.
1 or 8 per cent had extensive involvement of the left lung, particularly.

Sputum:
13 or 100 per cent were always positive.

Complications:
2 or 15 per cent had tuberculous laryngitis.
1 or 8 per cent had tuberculosis of the tongue.
1 or 8 per cent had spontaneous pneumothorax.

Treatment of Tuberculosis and Results:
10 or 76 per cent were treated with bed-rest only. Of these, 3 died of haemoptyses and 7 died of asthenia.
1 or 8 per cent had a right phrenic exeresis. Treatment ineffective; died of haemoptysis.
1 or 8 per cent had a left artificial pneumothorax, died of asthenia.
1 or 8 per cent had a right artificial pneumothorax, died of asthenia.

Average Blood Sugar:

5 or 38 per cent had 210 mg.
4 or 31 per cent had 275 mg.
4 or 31 per cent had over 300 mg.

Treatment of Diabetes:

12 or 96 per cent received insulin.
1 or 8 per cent did not receive insulin.

Causes of Death:

9 or 69 per cent died of asthenia.
4 or 31 per cent died of haemoptyses.

CONCLUSIONS

1. The incidence of the combination of diabetes and tuberculosis in the adult is so low that it is difficult to accept the assumption that diabetes predisposes to pulmonary tuberculosis, as is commonly believed. On the other hand, the fact that diabetes precedes tuberculosis in many cases leads one to suspect that this occurrence is more than a coincidence.

2. Diabetes following tuberculosis occurred infrequently, but in this series it was present more often than had been reported by others. It is my belief that diabetes in these cases occurred coincidentally and apparently had no relation to nor was precipitated by tuberculosis.

3. In the past few years, the number of admissions with diabetes and pulmonary tuberculosis has increased, perhaps due to the prolonged life span of the diabetic.

4. The pulmonary lesion was usually far advanced, caseous pneumonic and with an apico-caudal distribution, no part of the lung being spared. It was conspicuous by not being haematogenous. The extrapulmonary complications were chiefly tuberculosis of the larynx.

5. The advocates of the supposition that diabetes predisposes to pulmonary tuberculosis offer their explanation in the following theories, namely:

a. Hyperglycaemia
b. Acidosis
c. Increased glycerol production
d. Altered function of the leucocytes and tissues in general

It is my belief that a combination of these factors affects the immunobiological relationship between the tubercle bacillus and the host, in an already existent pulmonary tuberculosis, promoting the growth of the former and retarding the protective forces of the latter. Whether these

factors convert diabetics into potential tuberculosis patients is conjectural.

6. Tuberculosis became manifest in two distinct periods, early adult life and the middle age period. The large majority of the diabetic tuberculous died between the ages of forty and sixty.

7. In those who live with the combination, the majority have had their diabetes up to fourteen years, and their tuberculosis up to twelve years. In the group that died, the majority did not have their diabetes more than four years and tuberculosis more than two years. If they survived two years of the combination, the span was not more than eight years in the majority of cases.

8. The fact that the pulmonary lesion rarely goes on to spontaneous quiescence emphasizes the importance of early recognition and immediate collapse therapy. When the pulmonary tuberculosis is adequately controlled, the diabetes is more amenable to effective treatment. An active lesion, especially if it is accompanied by a persistent hyperpyrexia, disrupts the blood sugar balance and makes satisfactory maintenance difficult.

9. The most common cause of death was asthenia, which leads one to suspect that diabetes was a contributory factor, excluding an extrapulmonary tuberculous complication.

10. Finally, it is my observation that the course of pulmonary tuberculosis is altered in many cases, depending on the severity of the diabetes. The Jewish diabetic tuberculous patient does not do as well as his fellow nondiabetic. Although there are cases without diabetes that have a similar progressive course with the same unfavorable prognosis, the lesions are more fibrotic, of longer duration and slowly progressive. The combination restricts the period of longevity that would have occurred if either the diabetes or tuberculosis were absent, or both adequately under control.

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THE DECLINE IN MORTALITY FROM RESPIRATORY TUBERCULOSIS AMONGST YOUNG ADULTS[1]

G. PAYLING WRIGHT AND P. D'ARCY HART

The observation that there has been a retardation in the decline in the respiratory tuberculosis mortality of young women, as compared with those of other sex and age groups, in a number of countries in the present century has exercised the ingenuity of epidemiologists for some time. Widely different reasons have been suggested, but none so far has received general acceptance as an explanation either of its occurrence in particular countries or of its widespread appearance in many countries at more or less about the same time. The most recent suggestion of a generally applicable explanation, valid for England and Wales amongst other countries, for the retardation in the decline in mortality from this disease amongst young women, has been made by Wolff (4, 5). He believes that in most countries it was the result of the sharp rise in their birth rate in 1919 to 1922 that followed upon the unusually large number of marriages that took place in 1919, especially in the actively belligerent countries, as a consequence of postponement on account of the war of 1914 to 1918.

In England and Wales the retardation has been particularly pronounced, for it began soon after 1900 and has persisted with comparatively little change until quite recently. The causes of its onset in that country must, therefore, have come into partial, even if not into full, operation before that date, and any explanation offered for the phenomenon must take this crucial fact into account. There seem to be several reasons why Wolff's suggested explanation, whether applicable or not to other countries, cannot be accepted in the particular instance of England and Wales. These reasons are as follows:

1. *The discrepancies between the onset of the retardation in mortality decline and the alterations in the birth rate in England and Wales:* In chart 1 the curve for the respiratory tuberculosis mortality of young women, aged fifteen to twenty-four, is set out for comparison with the curve for

[1] From the Department of Pathology, Guy's Hospital Medical School, London.

the contemporaneous changes in the crude birth rate. There are several important points of difference between the courses followed by the two curves. For the first three decades after 1851 the phthisis mortality was falling rapidly while the birth rate was rising slightly. For the next two decades both were falling steadily. Between 1901 and 1919 the

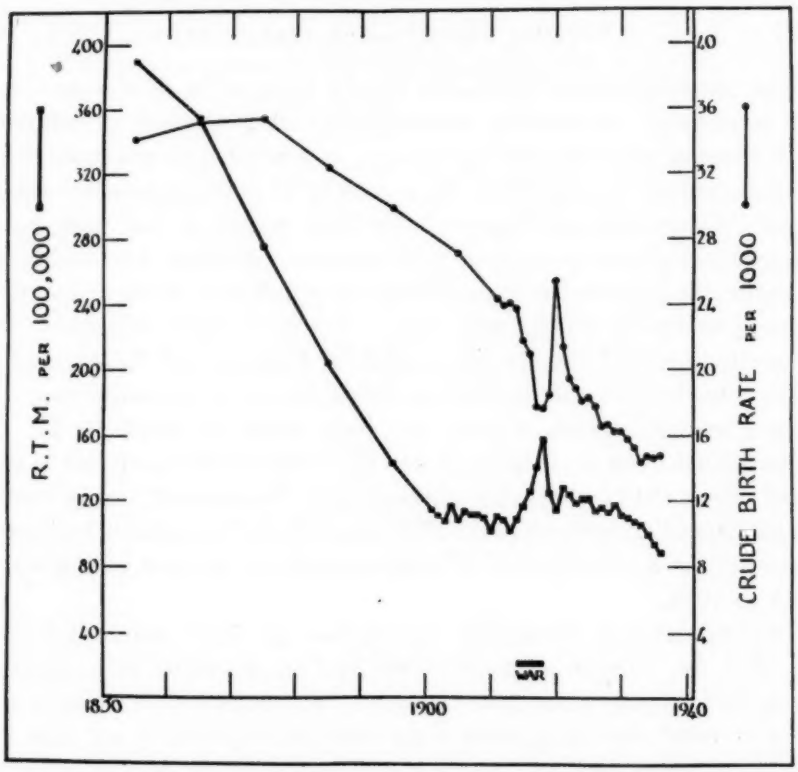

CHART 1. Respiratory tuberculosis mortality of young women, aged fifteen to twenty-four years, and crude birth rate from 1850 to 1936 in England and Wales.

birth rate was falling even faster than before, yet the phthisis mortality was more or less steady. A rapid rise took place in the phthisis mortality in the latter years of the war period and was followed by a correspondingly rapid fall to its former level. The rise in birth rate, to which attention has been directed by Wolff, was equally sharp and temporary, but it took place *two years after* the war-time rise in phthisis mortality. From such discrepant courses it seems difficult to infer that changes in birth rate have had much influence upon changes in respira-

tory tuberculosis mortality in England and Wales. The greatest discrepancy, of course, lies in the fact that the post-war rapid rise in the birth rate took place twenty years after the onset of the retardation in the decline in the mortality from that disease amongst young women.

2. *The fact that the retardation was very marked in the age group fifteen to twenty-four, an age at which comparatively few young women in England and Wales are married:* There has been a slow fall during the past half century in the proportion married amongst young women aged fifteen to twenty-four in England and Wales. It has fallen from about 19 per cent in 1871 to about 15 per cent in 1931, and at this latter date, of those 15 per cent well over nine-tenths were in the age group twenty to twenty-four (1). Wolff's suggestion, therefore, cannot explain the very marked retardation experienced by girls aged fifteen to nineteen, and even upon the supposition that pregnancy exerted an exceptionally deleterious influence on the respiratory tuberculosis mortality in the age group twenty to twenty-four, it would require the assumption that this disease runs an extraordinarily rapid clinical course under such circumstances. It seems scarcely credible that marriage, pregnancy, phthisis and demise should all be telescoped into so short a period as two or three years at the most, not in a few but in a very large number of cases.

3. *The fact that respiratory tuberculosis mortalities in England and Wales are substantially lower for married than for single women in the same age groups:* Even were pregnancy to result in greater liability to death from respiratory tuberculosis, there must be other factors associated with marriage that more than counteract this particular risk. The recent issue of the Decennial Supplement (Part II A, Occupational Mortality) of the Registrar General for England and Wales, contains for the first time comparative figures for the deaths from certain diseases of married and single women. In table 1 is set out a series of comparative mortalities from respiratory tuberculosis that have been calculated from the Registrar General's data not only for all married and all single women, but also for special groups of women in the various social categories ranging from Class I, the highest class economically, to Class V, the lowest. Apart from a few exceptions, which are mostly in those groups containing only a comparatively small number of married women, the mortality from this disease amongst single women is definitely higher than that found amongst the corresponding group of married women. The existence of a higher mortality amongst single women has also been observed in recent years in the County of London, where, according to

the Annual Report for 1931 of the Chief Medical Officer of Health (3), the rise in mortality from this disease amongst young women for a number of preceding years was almost exclusively confined to the unmarried.

4. *The occurrence of a set-back to the decline in respiratory tuberculosis mortality amongst young men as well as amongst young women in England*

TABLE 1

Average annual mortality from respiratory tuberculosis, per 100,000 living, amongst married and single women in various age groups during the triennium 1930 to 1932 in England and Wales

	AGES			
	16–19	20–24	25–34	35–44
All married women	102	105	87	66
All single women	103	127	124	83
Wives of occupied males	102	105	87	66
Single occupied women	82	113	114	77
Wives of unoccupied males	—	—	350	234
Single unoccupied women	183	198	164	101
Wives—Class I	—	—	41	31
Single women—Class I	—	—	—	—
Wives—Class II	—	67	56	44
Single women—Class II	63	67	68	41
Wives—Class III	98	103	86	65
Single women—Class III	74	107	116	82
Wives—Class IV	—	107	91	73
Single women—Class IV	110	151	149	95
Wives—Class V	132	126	114	90
Single women—Class V	106	148	115	100

No figure has been given when there were less than 20 deaths in the designated group during the whole triennium.

and Wales: The set-back to the decline in phthisis mortality amongst young men in England and Wales, although less marked than that amongst young women, shows that some cause apart from child-bearing has been operative.

Whatever effect the brief rise in the birth rate about 1919 to 1922 may have had upon the respiratory tuberculosis mortalities of young women

in other countries, there are thus no grounds for believing that it has played any important part in causing the retardation in the decline observed in England and Wales. As has been pointed out above, the causes of the retardation in that country must be sought in events that took place about 1900. At least three important social changes, two of them

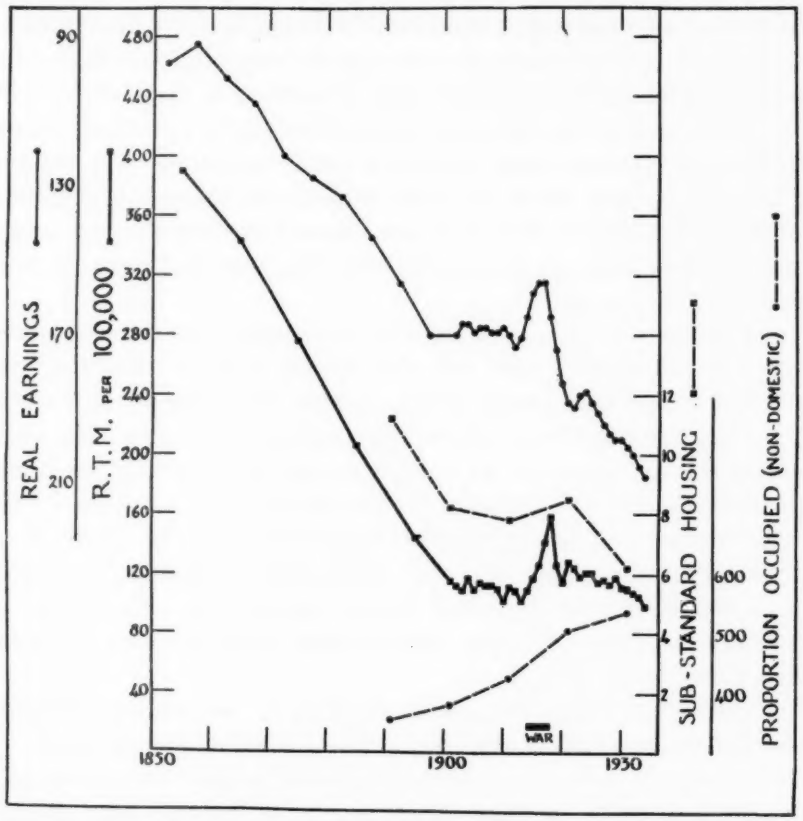

CHART 2. Respiratory tuberculosis mortality of young women, aged fifteen to twenty-four years, and real earnings from 1850 to 1936, together with substandard housing incidence and proportion occupied of young women, aged fifteen to twenty-four years, in nondomestic occupations, from 1891 to 1931, in England and Wales.

affecting all members of the community indiscriminately and one affecting young women specifically, took place about that date, *viz.*, (a) a prolonged check to the rise in the standard of living, as judged by real earnings, that had been taking place steadily during the preceding fifty years, (b) a slowing in the reduction in overcrowding, as judged by the Census housing returns and (c) an accelerated increase, particularly

marked in nondomestic employments, in the proportion of young women gainfully occupied, at a time when that for older women and for young men showed very little change (2). Taken over the secular period all three of these social changes have been important. The courses that they have followed are shown in chart 2, and the general similarity between the forms of these three curves and the curve depicting the changes in respiratory tuberculosis mortality in young women aged fifteen to twenty-four, appears much more strongly to favour the view that changes in these social conditions rather than alterations in the birth rate have exerted the deleterious influence upon phthisis in this particular sex and age group. At least these changes in social conditions have the merit of having occurred about the same time as the changes in respiratory tuberculosis mortality that they are believed to have affected, and not twenty years later as happened with the post-war changes in the birth rate.

The reason why certain of these social changes, that were common to both sexes and to all ages, fell with special severity upon respiratory tuberculosis amongst young adults, is believed by the present authors (2) to be attributable to a predisposing factor, *i.e.*, to a special sensitiveness of this age group to the conditions under which they are brought up during the formative years of adolescence and early adult life. "Their sensitiveness to social conditions is suggested to be due partly to the stress and strain arising from the environment of industry, and partly to biological changes occurring during adolescence. The latter possibly also account for young women being apparently more sensitive than young men."

A careful review of the whole problem of respiratory tuberculosis amongst young adults is especially important at the present time. The present war is likely to be accompanied by serious reductions in the standards of living in many countries, by widespread food shortage, by increase in overcrowding arising from lack of fuel and its enhancement by the lessened ventilation entailed by 'blackout' precautions, as well as, in the case of young women, by further marked increase in their industrial employment. The present analysis suggests that an adverse trend in respiratory tuberculosis mortality, especially amongst young adults, must be feared in the near future in consequence of these social changes, and that it will take place irrespectively of any alterations in the birth rate.

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THE SANATORIUM IN THE NEW JERSEY TUBERCULOSIS PROGRAM[1,2]

A Ten-Year Review

EMIL FRANKEL

DEVELOPMENT OF SANATORIUM CARE

The beginnings of the public sanatorium care for the tuberculous in New Jersey date back to 1907, when the New Jersey Sanatorium for Tuberculous Diseases at Glen Gardner was opened. The law creating the sanatorium stipulated that persons to be admitted "shall be afflicted with a tuberculous disease of the respiratory organs which is of a curable nature."

A law which became effective in 1912 made the counties responsible for the care of their tuberculous patients. The Board of Chosen Freeholders (the governing body of the county) is required to erect and maintain adequate hospital accommodations for tuberculosis patients in the county, and if the county has no tuberculosis hospital, to contract for their care elsewhere.

A state subsidy system for the maintenance of indigent tuberculous patients provides that the state pay $6 per week toward the cost of maintaining a county indigent patient and $12 per week for a state indigent patient. A county indigent patient is one who has resided in the county for five years; a state indigent patient has resided in the state for more than one year but has not resided in a county for five years.

BASIS OF PRESENT ANALYSIS

A comprehensive system of statistical reporting by the tuberculosis sanatoria to the New Jersey Department of Institutions and Agencies was inaugurated in 1929 and has enabled the Department to compile significant figures on the trend in sanatorium care during the last ten years. For each admission to a sanatorium there is submitted to the

[1] From the State Department of Institutions and Agencies, Trenton, New Jersey.

[2] Presented at the joint annual meeting of the New York Tuberculosis and Health Association and the Tuberculosis Sanatorium Conference of Metropolitan New York, New York City, March 5, 1940.

Department certain social data as well as the patient's final medical diagnosis. Pertinent medical data on discharge or death are likewise reported.

The basic findings in this study are derived from the information gleaned from the social and medical characteristics of patients admitted for the first time to sanatoria.

The information about first admissions over a period of years represents the most valid index of the prevailing policies with regard to the hospitalization of tuberculous patients. They afforded a measure for observing changes occurring in the make-up of the incoming patients in regard to sex, age, color, marital status, diagnosis, *etc.* In them are reflected the programs and efforts concerning the tuberculous of the local community.

TYPE OF PATIENTS ADMITTED

In 1939, 2,281 patients were admitted for the first time to the various state and county tuberculosis sanatoria in New Jersey. Of these 86.2 per cent were suffering from pulmonary tuberculosis, 1.9 per cent from other forms of tuberculosis and 11.9 per cent were classified as nontuberculous.

The table which follows illustrates the changing proportions in the different types of male and female patients admitted for the first time, and indicates that there is a growing number of adult nontuberculous patients entering state and county sanatoria. This increase has taken place in all the sanatoria but one and among both males and females, more among the former than among the latter.

YEAR	ADULT MALE FIRST ADMISSIONS			ADULT FEMALE FIRST ADMISSIONS		
	Per cent diagnosed as			Per cent diagnosed as		
	Pulmonary tuberculosis	Other forms of tuberculosis	No tuberculosis	Pulmonary tuberculosis	Other forms of tuberculosis	No tuberculosis
1939	84.0	2.4	13.6	88.9	1.4	9.7
1938	84.7	1.3	14.0	87.9	1.7	10.4
1937	88.0	1.2	10.8	88.9	1.1	10.0
1934	88.8	1.0	10.2	90.4	1.2	8.4
1929	96.7	1.3	2.0	97.7	0.9	1.4

Although an actual study of the individual cases can give the answer, various reasons may be suggested for the changes. The admissions may

be cases of bronchiectasis, lung abscesses and other chest conditions that can receive more appropriate care in a modernly equipped sanatorium than in a general hospital; they may be cases admitted and retained because there is no other public institution to which they can be transferred. More cases are being admitted by certain sanatoria for complete diagnostic study, not possible in the office of a private physician or a clinic. It is possible also that some communities may not have sufficiently accurate diagnostic facilities to screen out cases which should not be accepted for admission to sanatoria.

Diagnosis of pulmonary tuberculosis in first admissions: Figures on the classification of patients with pulmonary tuberculosis admitted to public sanatoria during the past ten years indicate that a larger proportion than in former years are diagnosed as "far advanced," a finding that at first glance would appear to contradict generally prevailing impressions.

1. Patients admitted with minimal tuberculosis decreased from 18.7 per cent of all first admissions in 1929 to 10.4 per cent in 1939.
2. Moderately advanced tuberculosis first admissions decreased from 40.7 per cent in 1929 to 29.8 per cent in 1939.
3. Far advanced tuberculosis first admissions increased from 40.6 per cent in 1929 to 59.8 per cent in 1939.

YEAR	TOTAL NUMBER	PER CENT OF PULMONARY TUBERCULOSIS FIRST ADMISSIONS DIAGNOSED		
		Minimal	Moderately advanced	Far advanced
1939	1965	10.4	29.8	59.8
1937	2036	10.0	28.4	61.6
1935	1980	12.0	34.2	53.8
1933	1910	13.1	36.3	50.6
1931	2315	15.8	37.5	46.7
1929	2199	18.7	40.7	40.6

It is extremely difficult to single out any one reason for this trend. Leading physicians, specializing in tuberculosis in the state, were consulted and the following reasons were suggested in explanation of this trend.

1. More accurate diagnostic measures based on larger experience with a fuller understanding of X-ray readings. Cases now diagnosed as minimal were frequently missed entirely and not classified as tuberculosis by earlier methods of presanatorium diagnosis (by clinics or private physicians). Cases now diagnosed as moderately advanced or even far advanced

may have shown only slight symptoms or signs on earlier stethoscopic examinations or interpretations of X-ray films.

2. Better facilities are available for the treatment of minimal cases in the community, if the danger of infection is absent, through private physicians, clinic services (diagnostic and pneumothorax) and follow-up. On the other hand, if the initial pneumothorax given in the community without hospitalization, refills and follow-up are not of the highest type or are not successful for other reasons, the disease will progress and the patient finally enters the sanatorium in a moderately advanced or far advanced, rather than minimal stage. The unfortunate attitude of some physicians who do not insist on aggressive treatment for symptomless minimal cases and are content to prescribe general health care, likewise decreases the number of early cases seeking hospitalization.

3. Institutionalization of far advanced cases has been stressed as a public health measure to prevent the spread of infection. Cases are now hospitalized who formerly were allowed to remain in their homes in a semi-moribund condition or were given treatment at home; and cases are diagnosed as far advanced and hospitalized who might not have been diagnosed before death in earlier years.

Age factor in pulmonary tuberculosis in first admissions: There are striking differences in the age distribution by sex of these first admissions to state and county sanatoria.

In 1939, 8 per cent of the males and 18 per cent of the females were under twenty years of age, 64 per cent of the males and 72 per cent of the females were at their most productive periods, twenty to forty-nine years of age, and 28 per cent of the males and 10 per cent of the females were over fifty years of age.

A different age grouping shows 41 per cent of the males and 72 per cent of the females under thirty-five, or 33 per cent of the males and 54 per cent of the females between twenty and thirty-four years of age.

YEAR	PER CENT OF PULMONARY FIRST ADMISSIONS IN AGE GROUPS							
	Male first admissions				Female first admissions			
	Under 20 years	20–34 years	35–49 years	50 years and over	Under 20 years	20–34 years	35–49 years	50 years and over
1939	7.7	33.2	30.6	28.5	17.8	53.9	18.6	9.7
1937	6.4	36.9	32.2	24.5	19.1	52.6	18.3	10.0
1935	8.4	39.3	32.1	20.2	17.3	54.8	20.8	7.1
1933	10.1	37.8	32.4	19.7	20.2	58.0	16.0	5.8
1931	10.6	37.5	32.6	19.3	22.1	56.1	16.6	5.2
1929	12.7	38.1	33.3	15.9	20.2	55.0	17.1	7.7

CASE REPORTING AND SANATORIUM ADMISSIONS

In 1938, 4,148 tuberculosis cases were reported to the State Department of Health and 2,043 entered state and county sanatoria; in 1929, 5,223 cases were reported and 2,224 entered sanatoria. This means

that almost one-half of all the tuberculosis cases reported to the State Department of Health in 1938 appeared on the roster of public tuberculosis sanatoria that year and that a growing proportion of cases officially reported are receiving public sanatorium care.

The increased use of the sanatoria is due to enlarged facilities for the care of patients in the state, general case-finding efforts and increased public consciousness of the value of sanatorium treatment as a curative procedure and as a preventive measure. This has been brought about by public health education of school, community and industrial groups, by both lay and professional agencies.

READMISSIONS TO SANATORIA

Among the 2,758 admissions to the public sanatoria in 1939 there were 27.2 per cent who had had previous sanatorium care. In 1929 readmissions were only 17.7 per cent. The trend has been toward a rising proportion of readmissions to tuberculosis sanatoria during the last ten years.

YEAR	TOTAL ADMISSIONS	PER CENT OF READMISSIONS IN TOTAL
1939	2758	27.2
1938	2731	25.2
1937	2743	24.8
1934	2604	20.9
1929	2702	17.7

In the opinion of the Committee on Tuberculosis of the Governor's Health and Welfare Conference the rising rate in readmissions "is doubtless influenced by the prevailing lack of facilities for after-care of patients. Failure to provide adequate relief allowances, with difficulty in obtaining suitable part time or full time employment under good working conditions may be responsible for this situation. Some large industrial firms pursue a generous policy on reëmployment of their own employees, but are loathe to employ workers not on their payroll previous to their illness. A large proportion of workers are unskilled and their education usually ended in the elementary grades. Their employment has often been of a seasonal or transient type."

DEATHS IN SANATORIA

The number of deaths occurring in sanatoria is closely tied up with the type of patients admitted and with the stage of disease of patients admitted with pulmonary tuberculosis. In the three year period 1937–1939, of 2,566 patients with pulmonary tuberculosis who died in sanatoria, 88 per cent were in the far advanced stages.

Measured by three different criteria, deaths in sanatoria have been kept at a low rate of occurrence in spite of an increasing number of patients under treatment, a rising number of patients admitted with far advanced tuberculosis and the introduction of surgical procedures involving considerable risks.

In the following table the sanatoria death rate is based (a) on the total under treatment during each year; (b) on the total first admissions and readmissions; and (c) on the far advanced first admissions and readmissions.

YEAR	SANATORIA DEATHS PER 100		
	Under treatment	First admissions and readmissions	Far advanced first admissions and readmissions
1939	15.5	28.8	50.1
1938	16.3	29.6	50.2
1937	16.7	29.9	51.0
1936	16.2	28.6	51.4
1935	16.3	28.7	56.8
1934	16.3	28.5	57.9
1933	16.3	28.8	59.4
1932	18.3	32.1	63.5
1931	17.2	28.1	60.3
1930	17.8	27.5	61.2
1929	17.3	26.4	64.0

Death reporting and sanatorium deaths: One of the most significant developments in the sanatorium field in recent years is the constantly increasing number of patients suffering from tuberculosis who die in sanatoria in comparison to the total tuberculosis deaths that occur and are reported in a given year, to the official state health agency.

In 1929, 2,917 tuberculosis deaths were reported to the State Department of Health and 724, or 24.8 per cent, of these occurred in public sanatoria. This may be contrasted with the situation in 1939 when a total of 1,821 deaths were reported and 846, or 46.5 per cent, took place in the sanatoria.

Between 1929 and 1939, total tuberculosis deaths reported to the State Department of Health decreased 37.6 per cent, tuberculosis deaths occurring in sanatoria increased 16.9 per cent.

YEAR	PERCENTAGE TUBERCULOSIS DEATHS IN SANATORIA OF TOTAL DEATHS REPORTED TO STATE DEPARTMENT OF HEALTH
1939	46.5
1938	44.3
1937	41.9
1936	36.6
1935	36.8
1934	35.7
1933	31.9
1932	33.1
1931	30.1
1930	29.3
1929	24.8

This hopeful change may be accounted for by the attitude of the sanatorium, the patient and the relatives. Only a few years ago some sanatoria sent moribund patients home to die because the patient and relatives requested it and because the death would not then be counted against the sanatorium. Today the importance of giving such patients active hospital care until death is recognized by all groups. This permanent segregation of infectious cases is one of the fundamental principles of tuberculosis control.

LENGTH OF SANATORIUM STAY

For every 100 patients under treatment in public sanatoria in recent years, from 36 to 39 returned to the community. During the last five years for every 100 patients admitted, from 66 to 69 were discharged.

A census taken of 2,739 resident patients in public sanatoria in June 30, 1939 showed that 40.9 per cent had a continuous stay of one year or more. The available figures indicate an increasing average length of stay of tuberculosis patients discharged alive from sanatoria, who have benefited from their treatment. This undoubtedly reflects institutional policies of prolonging the stay of patients in sanatoria to attain cure and also of the prevailing economic situation which makes the family less able and willing to care for, and support in the home, patients who cannot obtain work and may not be physically able to work.

Education before admission and during hospitalization has shown the

patient the value of prolonged care, and the danger to himself and his family of a return while still in the infectious stage.

There would naturally be a connection between the diagnosis of patients with pulmonary tuberculosis admitted to sanatoria and the average length of their sanatorium stay. The following table not only illustrates this connection but also the fact that the average stay has increased markedly in moderately and far advanced cases in the years under observation.

YEAR	AVERAGE (MEDIAN) DAYS OF SANATORIUM STAY OF PATIENTS DISCHARGED ALIVE AND ADMITTED AS			
	Pulmonary patients	Minimal	Moderately advanced	Far advanced
1939	226	151	233	249
1937	194	133	235	188
1935	195	124	236	193
1933	194	132	252	180
1931	159	148	168	153
1929	135	127	151	110

As would be expected the average stay in sanatoria of discharged patients is relatively longest for those whose health condition on leaving is most nearly restored to normal. In 1929, the unimproved patients stayed 72 days and in 1939, 81 days. Patients discharged as improved or better stayed 265 days in 1939, in contrast to 159 days in 1929.

CONDITION ON DISCHARGE	AVERAGE (MEDIAN) DAYS OF SANATORIUM STAY	
	1937–1939	1929–1931
All patients	203	145
Arrested	363	267
Apparently arrested	346	240
Quiescent	254	234
Improved	186	129
Unimproved	79	75

As in the case of discharges the length of stay of those dying in sanatoria has been considerably increased in recent years. In 1929, 71.9 per cent of those who died in sanatoria did so in less than six months, while only 13.8 per cent stayed a year or more. This may be contrasted with the 1939 situation when 62 per cent died within six months, but 22.7 per cent remained a year or more.

IMPORTANCE OF THE SANATORIUM IN TUBERCULOSIS CONTROL

There is general agreement that it is exceedingly difficult to single out any one factor to which may be attributed the dramatic decrease in the incidence of tuberculosis in the general population. It has been asserted that the general improvement in economic and social conditions during the last few decades has been as important as the tuberculosis control movement in which the sanatorium has played so important a part.

Nevertheless there is universal recognition that since tuberculosis is transmitted by infection among persons in close contact with the individual patient, isolation achieved through institutional care has become of prime importance to stop the sources of infection.

Past experience indicates that the tuberculosis sanatorium will continue to occupy an important place in the movement toward combating tuberculosis. This movement—well organized and comprehensive—will lead toward the eventual eradication of tuberculosis, as now seems confidently to be expected. It is extremely desirable, therefore, that the sanatorium continue to receive adequate community support; that it be given every encouragement to go on with its curative work as well is to experiment with measures which will act as effective health restoratives of patients suffering from tuberculosis, and lead toward the discovery of new measures of tuberculosis control.

TUBERCULOSIS IN MENTAL HOSPITALS[1]

M. POLLAK,[2] A. V. HUMMEL[3] AND I. L. TUROW[3]

This report deals with a survey conducted from October 1, 1937 to December 22, 1939, at the Peoria State Hospital, a mental institution with an average daily census of 2,575 patients.

This hospital, since 1905, has had a tuberculosis division. As a matter of fact, its "tent colony," erected by its first managing officer, the late Dr. George A. Zeller, was the first public, and is the second oldest, tuberculosis sanatorium in our State. It is evident, therefore, that tuberculosis has always been given considerable attention in this institution. The X-ray examination of the 56 patients on the tuberculosis division, however, showed that 9, or 16 per cent, had no tuberculosis. Thus of the 2,510 resident patients in the hospital at the beginning of the survey only 47, or 1.87 per cent, were known to have tuberculosis.

It is of interest to note here that one of the nontuberculous cases died shortly after an X-ray film had been taken and before we had an opportunity to study it. On the death certificate, however, tuberculosis was given as the cause of death.

From the very beginning of the survey, the attention of the hospital staff was directed towards the importance of X-ray examination in diagnosis, and it was made obligatory to take a chest roentgenogram on all patients who were transferred to the infirmaries, irrespective of whether tuberculosis was suspected or not. Many cases of tuberculosis were discovered by this procedure. One of these is particularly illuminating.

A patient was transferred to the infirmary, because he presented a difficult feeding problem. The X-ray film revealed far advanced pulmonary tuberculosis and a localized pneumothorax. The patient died shortly after the transfer. Without the roentgenogram, no doubt, the cause of death would have been given not as tuberculosis.

[1] Presented at a session of the Medical Section at the 35th annual meeting of the American Trudeau Society, Cleveland, Ohio, June 3, 1940.

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In the course of our study, we surveyed 2,156 patients in residence, 766 patients newly admitted to the Receiving Wards and 477 employees. For the Mantoux test we used PPD in the two standard strengths on the majority of the resident patients and employees, and 0.1 mg. and 1 mg. OT on the majority of Receiving-Ward patients. The 56 patients found on the two tuberculosis wards, 27 others among the resident patients and 100 patients on the Receiving Wards were not tuberculin tested but X-rayed only. For the radiographic study 14 x 17″ single celluloid films were made.

Of the 2,129 resident patients tuberculin tested, 2,016, or 94.6 per cent, gave a reaction, of the 666 Receiving-Ward patients, 537, or 80.6 per

TABLE 1

Age groups

AGE GROUPS IN YEARS	RESIDENT PATIENTS		RECEIVING-WARD PATIENTS		EMPLOYEES	
	Number	Per cent of group	Number	Per cent of group	Number	Per cent of group
0–19	5	0.2	24	3.1	0	0
20–29	57	2.6	101	13.1	128	26.8
30–39	203	9.4	128	16.7	133	27.8
40–49	388	17.9	139	18.1	119	24.9
50–59	583	27.	160	20.8	72	15.
60 and over	904	41.9	209	27.2	25	5.2
Age unknown	16	0.7	5	0.6	0	0
Total.....	2,156	99.7	766	99.6	477	99.7

cent, and of the 448 employees, 257, or 57.3 per cent. Of the 2,156 resident patients X-rayed, 242, or 11.2 per cent, of the 766 Receiving-Ward patients, 57, or 7.4 per cent, and of the 477 employees, 8, or 1.6 per cent, showed parenchymal lesions.

The three groups varied in reference to age. The majority, 68.9 per cent, of the resident patients were over fifty years old, while of the Receiving-Ward patients 48.1 per cent, and of the employees only 20.3 per cent belonged to this age group (table 1).

Of the 2,156 resident patients 1,045, or 48.4 per cent, were males. Of the 766 Receiving-Ward patients 506, or 66.5 per cent, were males. Among the resident patients 12.1 per cent of the males and 10.3 per cent of the females had tuberculosis. Among the Receiving-Ward patients 6.9 per cent of the males and 8.4 per cent of the females had the disease.

Of the resident patients 96.3 per cent were white. Of the Receiving-Ward patients 96.8 per cent were white. Of the white resident patients 11.2 per cent had tuberculosis and in the colored group 11.4 per cent. Of the white Receiving-Ward patients 7.1 per cent had tuberculosis and in the colored group, 16.6 per cent. Obviously the colored group is too small in number to permit any true comparison with the white patients.

Tuberculosis was found among all age groups in a significant percentage (table 2).

The study of the length of residence in the institution of the tuberculous patients revealed the fact that the percentage of the tuberculous increased in accordance with the length of the stay of the patients.

TABLE 2

Incidence of tuberculosis according to age groups

AGE GROUPS IN YEARS	RESIDENT PATIENTS			RECEIVING-WARD PATIENTS			EMPLOYEES		
	Number examined	Number tuberculous	Per cent tuberculous	Number examined	Number tuberculous	Per cent tuberculous	Number examined	Number tuberculous	Per cent tuberculous
10–19	5	0	0	24	0	0	0	0	0
20–29	57	16	28.0	101	5	4.9	125	4	3.2
30–39	203	36	17.7	128	9	7.0	130	1	0.7
40–49	388	50	12.8	139	9	6.4	114	2	1.7
50–59	583	62	10.6	160	17	10.6	72	1	1.3
60 and over	904	73	8.0	209	16	7.6	25	0	0
Age unknown	16	5	31.2	5	1	20.	11	0	0
Total.....	2,156	242	11.2	766	57	7.4	477	8	1.6

Because of the relatively few individuals examined and cases found the percentages are not as significant among the employees. But it is evident that one-half of the tuberculous developed the disease after five years of service (table 3).

Of the 8 tuberculous employees, 7 belonged to the group of 381 who were in close contact with the patients, such as doctors, nurses and attendants. The percentage of tuberculosis in this group was 1.8 per cent, not significantly higher than in the total group.

The percentage of the tuberculous varied somewhat in the different psychotic groups (table 4).

Of the 57 tuberculous patients on the Receiving Wards, 6, or 10.5 per cent, were committed from tuberculosis sanatoria, and of an additional 8 patients, or 14 per cent, it was known that they had tuberculosis at

TABLE 3

Length of residence of tuberculous patients and length of service of tuberculous employees at the time of diagnosis

LENGTH OF RESIDENCE OR SERVICE IN YEARS	TUBERCULOUS PATIENTS		TUBERCULOUS EMPLOYEES	
	Number	Per cent	Number	Per cent
0–½	1	0.4	0	0
½–1	3	1.2	1	12.5
1–2	13	5.3	3	37.5
2–5	29	11.9	0	0
5–9	37	15.2	3	37.5
10–19	102	42.1	1	12.5
20 and over	57	23.5	0	0
Total	242	100.	8	100.

TABLE 4

Psychotic groups

PSYCHIATRIC DIAGNOSIS	RESIDENT PATIENTS				RECEIVING-WARD PATIENTS			
	Examined		Tuberculous		Examined		Tuberculous	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
Schizophrenia	1,422	65.9	178	12.5	126	16.4	6	4.7
Manic-depressive	92	4.2	10	10.8	37	4.8	0	0
Psychosis due to arterial disease	90	4.1	8	8.8	66	8.6	7	10.6
Psychosis due to mental deficiency	39	1.8	6	15.3	3	0.3	1	33.3
Psychosis due to syphilis	102	4.7	9	8.8	52	6.7	2	3.8
Psychosis due to other somatic diseases	11	0.5	2	18.1	5	0.6	1	20.
Psychosis due to epilepsy	32	1.4	3	9.3	5	0.6	0	0
Psychosis due to alcohol	39	1.8	4	10.2	39	5.0	3	7.6
Without psychosis	311	14.4	22	7.6	378	49.3	34	8.9
Undiagnosed	18	0.8	0	0	55	7.1	3	5.4
Total	2,156	99.6	242	11.2	766	99.4	57	7.4

TABLE 5

Disposition of tuberculous patients by January 1, 1940

GROUP	NUMBER	PER CENT OF TOTAL	DIED		DISCHARGED OR PAROLED		IN HOSPITAL	
			Number	Per cent	Number	Per cent	Number	Per cent
Old tuberculosis wards	47	13.5	22	46.8	1	2.1	24	51.
General wards	242	69.9	23	9.5	4	1.6	215	88.8
Receiving wards	57	16.4	12	21.	19	33.3	26	45.6
Total	346	99.9	57	16.4	23	6.6	265	76.5

the time of admission. Therefore, only 43 new cases were discovered in the course of the survey, giving a ratio of 5.7 per cent among 752 Receiving-Ward patients surveyed.

We were interested in the status of our tuberculous group in reference to their commitment. Of the 346 tuberculosis patients under discussion, 282, or 81.5 per cent, were involuntarily committed, and 64, or 18.4 per cent, were admitted under voluntary commitment.

By January 1, 1940, of the 346 tuberculous patients, 57, or 16.4 per cent, were dead, 24, or 6.9 per cent, discharged or paroled and 265, or 76.5 per cent, still in the hospital (table 5).

DISCUSSION

In the State of Illinois considerable interest has always been evidenced in the problem of tuberculosis control in mental institutions. At the early date of October 18, 1906, at the Conference of Superintendents of the State Hospitals, presided over by Frank Billings, W. A. Evans (1) stated that by physical examination alone many of the early cases are missed, and advocated the use of the tuberculin test for diagnosis, the examination of every patient on admission and annually thereafter.

Only recently in the course of a new building program in its mental institutions this State spent $525,000 on the erection of new tuberculosis units in the different State Hospitals.

Recent studies by Bogen, Tietz and Grace (2), McGhee and Brink (3), Burns (4), Leonidoff (5), Leader (6), Wicks (7) and others have shown that tuberculosis in mental institutions is more prevalent than mortality statistics would indicate. The fact that 5.2 per cent of the people who die of tuberculosis annually in the U. S. A. die in mental institutions, while only 15.9 per cent in tuberculosis hospitals (8), reflects clearly the magnitude of the problem from a national angle.

In our study we found that in using physical examination alone, tuberculosis is at times diagnosed when it does not exist, and overlooked at others even in the terminal stage. Leonidoff (4), too, found in his survey that 38 per cent of the patients on the tuberculosis wards had no tuberculosis. In 100 consecutive autopsies conducted at the Manteno (Illinois) State Hospital, Kirshbaum (9) found 17 cases who died of tuberculosis, 5 of which were not diagnosed antemortem, and 6 others with active disease whose condition was not recognized prior to death. In the Anna (Illinois) State Hospital, Stanka (10) in 50 autopsies found 2 undiagnosed cases of tuberculosis. It must happen, therefore, fairly often that tuberculosis is overlooked in mental hospitals.

The different infection rates observed in the three groups under discussion (resident patients, Receiving-Ward patients and employees) has to be attributed, we believe, to the difference in the age groups, and the high percentage of positive reactors among the resident patients chiefly to advanced age. It should be considered also that the patients of our hospital are recruited from a population stratum (low income group and laborers) in which *per se* the infection and morbidity rates are high.

There was a significant difference in the percentage of tuberculosis among the resident patients, 11.2 per cent, and among the Receiving-Ward patients, 5.7 per cent (figuring in the latter group only the newly discovered cases). These rates, as well as the fact that the percentage of the tuberculous increases in accordance with the length of residence of the patients in the institution proves the fact that many of the patients develop tuberculosis while they reside in the institution. Whether the disease develops through the endogenous or exogenous route may be argued. It cannot be denied, however, that while patients are taken care of in a medical institution for their mental ailment, their tuberculosis is not diagnosed, unless special efforts by systematic surveys are made towards this end.

The percentage of positive reactors and cases discovered by means of tuberculosis surveys varies considerably according to various authors. Burns' (4) records show 10.6 per cent tuberculous among 8,969 hospital inmates. Wicks (7) among 10,816 hospital patients found 7.3 per cent with significant lesions and an additional 7.5 per cent with "definitely or probably arrested" lesions.

It is of significance that in the six hospitals reported upon by Burns the percentage of the tuberculous varied from 3 per cent to 12.5 per cent. In the series of Wicks this variation was from 3.1 per cent to 11 per cent for the significant lesions, and from 1 per cent to 11 per cent additional for the "definitely or probably arrested" lesions.

Manifestly some important differences must exist between these various institutions either in respect to the type of patients admitted or in regard to their management, or both. A detailed study of these differences could lead, we believe, to some important and valuable information concerning tuberculosis in mental hospitals.

In our employee group the percentage of the tuberculous, 1.6 per cent, was low, as against 3.7 per cent found by Burns and 2.1 per cent by Wicks. The systematic tuberculosis survey conducted among the nurses since the year 1933, and the fact that in our institution patients are used extensively on ward services, may explain this low rate, we believe.

The development of tuberculosis among the employees deserves serious consideration. Here again the question of endogenous or exogenous reinfection can be debated. But hospital authorities cannot evade the responsibility for the fact that employees of a mental institution develop tuberculosis without anyone's awareness of it.

Moreover, under the ever-widening scope of the various Occupational Disease Acts, tuberculosis among hospital personnel is being considered as an occupational hazard with increasing frequency. While it cannot be proved that in a given case the disease developed by the exogenous route, some courts as shown by Kletzsh (11) have already awarded considerable sums in compensation for such claims. Such a claim has already been presented by an employee of our hospital, whose disease was discovered by our survey. The best prevention against such claims consists in the proper segregation of the tuberculosis patients and in the regular systematic survey of all employees.

The rationale of spending money on tuberculosis prevention among the psychotics, who already represent a tremendous burden on society, was seriously questioned by some authorities in the course of our study. The fact, however, that 6.9 per cent of our tuberculous patients have already been discharged or paroled by January 1, 1940, shows that some of these patients have an opportunity to spread their disease in their own family and community after they return home. The possibility of the spread of the disease from these patients to the employees has also to be considered seriously. For these reasons the money spent on tuberculosis prevention must be considered as a prudent investment on the part of hospital authorities.

TREATMENT

The treatment of the tuberculous psychotic differs in no way from that of the mentally normal. Rest should be as rigidly enforced as is possible with this type of patient. Sedation might have to be resorted to at times, and for this purpose we prefer the use of the barbiturates in appropriate doses. In the course of our survey we had opportunity to observe considerable improvement in some of our patients' condition under a rest regimen, even in advanced cases.

Our chief aim in treatment is to convert the sputum and thereby lessen the possibility of the spread of infection. For this reason we make use of collapse therapy even if the patient's mental condition seems to be entirely hopeless.

From our experience thus far, we believe, that the treatment of the tuberculous psychotics offers comparable results to that of our mentally normal patients.

Patients under shock therapy deserve special consideration. In our series we observed 188 patients under this type of treatment. Of these 6, or 3.2 per cent, developed tuberculosis either during the course or after the treatment. This fact warrants the requirement that patients should be X-rayed immediately before undergoing shock therapy and frequently thereafter.

ADMINISTRATION

In reference to administration it has to be considered whether or not the tuberculous psychotics of a state system should, or should not be centralized in one institution. Our State Welfare Department, which has the State Hospitals under its jurisdiction, has taken a stand against such centralization, chiefly because it would be costly by necessitating the transportation of the patients to a considerable distance from their homes, and secondly, because such a system would entail considerable hardship when the family would have to travel long distances to visit the patients. We believe that these are valid reasons in favor of decentralized care. Moreover, in all hospitals of our State we have already tuberculosis units which can be fully untilized for the care of the tuberculous.

Under decentralization, however, each hospital has to have on its staff at least one physician who is well trained in psychiatry as well as phthisiotherapy. While such combination in physicians is not common as yet, we believe that their training does not present unsurmountable difficulties. Moreover, the training of such physicians promises worth while contributions to the psychiatric as well as to the tuberculosis field. It is imperative, however, that these resident physicians work under the supervision and direction of tuberculosis experts who may be located at a central place and from there make regular visits to the hospitals.

All our hospitals have an X-ray laboratory. Some of these, perhaps, will be found in need of improvements, but these should prove not very costly. The roentgenograms taken at the different hospitals showing pathological changes after a preliminary scrutiny by the resident, should be submitted to the tuberculosis expert for his final diagnosis and recommendation for treatment.

By such an arrangement an efficient and economical tuberculosis service can readily be established in every institution.

CONCLUSIONS

1. Tuberculosis is a problem of first order in every mental institution.

2. Patients suffering from tuberculosis are admitted to these institutions in a fairly large percentage without being so diagnosed. In addition to these, a relatively large percentage of patients develop tuberculosis while in residence, again without their disease being recognized.

3. Due to the contagious nature of tuberculosis, mental institutions should develop a definite and systematic tuberculosis control program, employing the tuberculin test and X-ray in diagnosis. These examinations should be conducted on all newly admitted patients immediately after admission and on the resident patients at least once annually.

4. Collapse therapy should be fully utilized in the treatment of the tuberculous psychotic, irrespective of the patient's mental deterioration.

5. Patients selected for shock therapy should be X-rayed before commencing treatment and re-rayed at frequent intervals during and after such treatment.

6. Employees coming in close contact with the patients should be X-rayed every three months and the tuberculin reactors among the other personnel at least once annually.

We wish to express our thanks and appreciation to Mr. A. L. Bowen, Director of the Department of Public Welfare, for having made this survey possible and for his deep interest in our work; to Walter H. Baer, M.D., Managing Officer of the Hospital, for his sincere coöperation and to Mrs. Louise Edmonson for her painstaking work in tabulating the statistical data.

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THE PREVENTORIUM AND REINFECTION TYPE TUBERCULOSIS

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This study was undertaken to determine the effect of preventorium care on prevention of reinfection or adult type tuberculosis in children with first infection or childhood type tuberculosis. This study was considered particularly interesting at this time because in recent years several communications have appeared in the field of tuberculosis by eminent authorities who expressed the view that, as a rule, children with primary tuberculosis need no special treatment and that treatment has little value in lessening the incidence of adult type disease. Thus Ch'iu, Myers and Stewart (1) state, "Treatment of children with primary complex has not been found to afford any more protection against the clinical type of tuberculosis in adult life than similar treatment would be expected to prove against tertiary syphilis years later for persons with primary syphilis."

Theoretically, one would expect, if general care such as proper food, vitamins, fresh air and rest are beneficial in active tuberculosis, similar treatment should be helpful in stabilizing a relatively benign primary lesion and preventing development of active tuberculosis later. Experience during and immediately after the World War showed very definitely that mortality and morbidity of tuberculosis varied in direct proportion with the extent of malnutrition, overexertion and lack of hygienic surroundings.

It is quite obvious, of course, that a large number—if not the vast majority of primary lesions—heal without any supervision or special treatment, and do not develop into disseminated or reinfection type tuberculosis. We have also found that in most benign cases without signs or symptoms we can demonstrate virulent tubercle bacilli, undoubtedly from unhealed tuberculous foci, by gastric lavage and guinea pig inoculations (2).

What we would like to determine is whether good care and supervision

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would further increase the percentage of healed primary foci and thus diminish the incidence of adult type tuberculosis. A careful survey of children with primary tuberculous infections who had the benefit of general treatment over a long period of time (especially if compared with similar groups who did not have such treatment) ought to give us some valuable information.

In this discussion we are dealing with this type of case. All of the children have been patients at Prendergast Preventorium, all have had a history of contact with open tuberculosis, all have had positive tuberculin tests. While a few showed primary calcified nodules in the lung or calcified lymph nodes in the hilum, none showed active disease. All children had adequate general care while at the preventorium and intensive follow-up work at home where the same routine was carried out as far as possible as at the preventorium. All of this information was gathered under the personal supervision of Miss Billings and only those who gave reliable information were included in this survey.

This communication is based on a follow-up study of 1390 children who were discharged from the Prendergast Preventorium during the last sixteen years. A large number of these children are now older than nineteen, the average age when children with primary tuberculous infection develop clinical pulmonary tuberculosis. We should, therefore, be able to get a fairly good idea of the value of preventorium care in the early years for prevention of active tuberculosis during the 'teen age and beyond.

Since the institution opened in 1922, there have been 1390 children discharged from Prendergast Preventorium; 283 of these children remained at the preventorium less than six weeks and were not included in the study; 128 children could not be located (24 of these live in Boston and were known to have visited clinics from time to time but the data were too incomplete for consideration). Sixty-five children moved away from Boston. This left 914 children who were living in Boston and on whom we had complete histories.

Table 1 shows the results of our findings according to the length of observation. In summary, the 914 children may be divided into two subgroups, children followed at least ten years and children followed less than ten years. In the group followed for the longer period of time are 409 children and in this group 9 children have developed tuberculosis (2 of these children died of this disease). The average number of years of follow-up in this group was thirteen. In this group there was an

incidence of 2.2 per cent (3.2 per cent in girls and 0.6 per cent in boys). This is a much lower proportion of breakdown with tuberculosis than has been reported for tuberculin-positive children in general. In a

TABLE 1

Development of tuberculosis in preventorium treated children

1922–1939

ON ADMISSION TO PREVENTORIUM					AT END OF FOLLOW-UP PERIOD		
Admission Year	Total Number	Average Age	Sex		Average Age	Developed Pulmonary Tuberculosis	
			F	M		Female	Male
1922	21	8	21	0	25	3 (1 d. '30)	0
1923	15	9	15	0	24	0	0
1924	60	8	32	28	23	0	1
1925	47	8	32	15	22	1	0
1926	49	8	33	16	21	0	0
1927	45	8	25	20	20	0	0
1928	41	8	19	22	19	1 (d. '36)	0
1929	79	7	42	37	17	2	0
1930	52	7	34	18	16	1	0
Total.....	409	8	253	156	21	8 (2 died)	1
Developed tuberculosis....	9—2.2%		8—3.2%	1—0.64%			
1931	76	8	39	37	16	0	0
1932	80	8	35	45	15	0	1
1933	53	8	20	33	14	0	1
1934	68	9	38	30	12	1	0
1935	54	8	24	30	12	0	0
1936	46	8	22	24	11	0	0
1937	72	8	36	36	10	0	0
1938	56	9	31	25	10	0	0
Total.....	505	8	245	260	12	1	2
Developed tuberculosis....	3—0.6%		1—0.4%	2—0.8%			
Grand total....	914		498	416	20	9	3
Developed tuberculosis...	12—1.3%		9—1.8%	3—0.7%			

group of 446 untreated tuberculin-positive children who were approximately in the same age group and followed approximately the same number of years (11.3 years) as our children at the preventorium, Ch'iu, Myers and Stewart (1) found 45 sick with tuberculosis and 22 dead of this

disease, a total of 67 or 15.02 per cent. Pope *et al.* (3) reported a cumulative tuberculosis morbidity of 6.4 per cent in tuberculin-positive children who were followed for a period of ten years or more in about the same age group. The rate was twice as high in girls as in boys (8 per cent in girls and 4 per cent in boys).

We realize, of course, that a report from parents and neighbors that the children are well does not rule out asymptomatic adult type tuberculosis. However, there cannot be asymptomatic deaths and a mortality of 2 in 409 cases is obviously much lower than 22 out of 446 as reported by Ch'iu, Myers and Stewart (1).

In a disease such as tuberculosis, with so many variable factors to consider, it is impossible, of course, to draw any conclusion at to what factor or factors contributed most to the results. It is quite possible that at Prendergast Preventorium we happened to strike upon the optimum age (six to twelve years) to concentrate on building up resistance in children with primary tuberculous infection, an age at which the natural resistance to this disease is the greatest. From our findings it would seem fair to assume that preventorium care, proper diet, hygiene, removal of foci of infection and supervision after discharge has obviously had some beneficial effect directly or indirectly upon the prevention of subsequent development of clinical tuberculosis.

SUMMARY AND CONCLUSION

A careful survey was made of 914 children with primary tuberculous infection who were discharged from the Prendergast Preventorium during the last sixteen years. The low proportion of breakdown with pulmonary tuberculosis and of death from pulmonary tuberculosis is striking when compared with groups reported by other observers.

Preventorium care of children between the ages of six and twelve seems to have a noticeable influence on the prevention of the reinfection-type tuberculosis during adolescence.

While it is impossible to admit to a preventorium every child who has a positive tuberculin test, it would seem that the least we should do is to try to approximate preventorium care in the home for every case of primary tuberculous infection, in addition to removing any open case of tuberculosis from the home.

Further observation of the effect of preventorium care on a larger number of children with primary tuberculous infection over a longer period of time is certainly justified, especially in localities where sana-

torium beds are available and there is no urgent need of converting the preventorium into a sanatorium.

Those who deprecate the value of the preventorium in the tuberculosis campaign should at least produce more convincing data to prove their contention.

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TUBERCULOSIS OF TONSILS[1]

Its Relation in Children with Tubercle Bacilli in Gastric Contents

E. ROSENCRANTZ AND SAMUEL HURWITZ

This study was undertaken in conjunction with an investigation of guinea pig inoculation of the gastric contents of tuberculous children (1). Recent literature has many references to tuberculosis of the tonsils revealed by routine examination of clinically nontuberculous patients and tuberculous adults; however, there is very little written about the tonsils of tuberculous children and nothing, as far as we could find, on the association of tuberculous tonsils and positive gastric contents.

As early as 1875 Cornil (2) observed tuberculous ulceration of the tonsils clinically. Isolated cases have since been reported (3). However, the rarity of this so-called manifest or clinical type of tonsillar tuberculosis is shown by the fact that Brown (4) could find only 57 such cases recorded in the literature up to 1937.

The earliest recognition of latent tonsillar tuberculosis is attributed to Dieulafoy (5), who in 1895, by animal inoculation found the tonsils to contain tubercle bacilli in 13 per cent of patients without clinical evidence of tuberculosis. Later, histological evidence of tuberculosis of the tonsils was observed; all of the recent reports on the incidence of this condition are based on microscopical examination.

In a collected series of 30,676 tonsillectomies quoted by Newhart (6) the incidence of tuberculosis of tonsils was 2.03 per cent. The author believes that about 1 per cent of routine tonsillectomies will reveal tuberculosis on microscopical examination. The frequency of tuberculous tonsils in adults with pulmonary tuberculosis has been stated by various observers (7) to be between 40 and 70 per cent; it occurs most frequently among patients with extensive pulmonary involvement. It is claimed, furthermore, that serial sections of the tonsils will reveal a higher incidence of tuberculosis than routine microscopical examination (6).

[1] From the Departments of Medicine and Pediatrics, University of California Medical School, and the Department of Public Health, San Francisco, California.

MATERIAL

Our group consists of 103 female children ranging in age from eight months to thirteen years who were admitted to the University of California Tuberculosis Service at the San Francisco Hospital during the past five years. In each case the Mantoux test with 0.1 mg. OT was positive. The gastric contents of each child were injected into a guinea

TABLE 1

Patients with tuberculosis of tonsils

NUMBER	AGE	X-RAY EXAMINATION	GUINEA PIG INOCULATION GASTRIC CONTENTS
1	12	Infiltration right upper lobe	Positive
2	6	Enlarged hilar lymph nodes	Positive
3	3½	Infiltration left upper lobe	Positive
4	7	Infiltration right lower lobe	Positive
5	3	Enlarged hilar lymph nodes—Potts disease	Positive
6	10	Pleural effusion	Positive
7	2¾	Infiltration right upper lobe	Positive
8	12	Enlarged cervical lymph nodes Enlarged hilar lymph nodes	Positive
9	8	Enlarged cervical lymph nodes Bone tuberculosis Enlarged hilar lymph nodes	Positive
10	12	Pleural effusion	Positive
11	3	Infiltration right upper lobe	Positive
12	5	Enlarged hilar lymph nodes	Positive
13	1½	Infiltration right upper lobe	Positive
14	6	Infiltration left upper lobe	Positive
15	6	Infiltration left upper lobe	Positive
16	4	Enlarged hilar lymph nodes	Positive
17	2½	Enlarged hilar lymph nodes	Positive
18	3	Enlarged hilar lymph nodes	Positive
19	6	Enlarged hilar lymph nodes	Negative

pig according to the method described elsewhere (1). An X-ray film was taken of each child. Many of these patients had hypertrophic tonsillitis; therefore, when the general condition had improved, tonsillectomy and adenectomy were done as indicated. Microscopical examination of the adeno-tonsillar tissue was done by the pathology department.[2]

The pathological lesions are either unilateral or bilateral and the tuber-

[2] We wish to render our thanks to Dr. Jesse Carr for his data on the pathological findings.

cle formation is either discrete or confluent. Giant cell formation is common, but caseation is not a marked feature. The surface epithelium of the tonsil is invariably intact, tubercle bacilli are rarely demonstrated. In one case the adenoid tissue alone showed tuberculous involvement.

Table 1 lists the salient clinical points in the patients with tuberculosis of the tonsils. The ages range from sixteen months to twelve years. Clinical pulmonary tuberculosis was diagnosed in 8 patients and corroborated by X-ray findings. In the remaining group, hilar lymph node enlargement occurred in 9 patients, pleural effusion in 2, cervical lymphadenitis twice in association with hilar nodes and an additional complication of bone tuberculosis in one of the latter patients.

Out of the 103 patients whose tonsils were microscopically examined, 19 or 18.4 per cent showed tuberculous involvement. Of these 19 patients, 18 had positive gastric contents as shown by guinea pig inoculation.

In every case following tonsillectomy the recovery was normal. The operation was deferred until the pulmonary lesion was in a quiescent stage and until there was a general improvement in the physical condition of the patient. There were no special operative procedures necessary in these patients. The postoperative course was quite uneventful.

DISCUSSION

Preoperative diagnosis of tuberculosis of the tonsils was impossible in this series as there was no clinical evidence of a tonsillar lesion. Most observers have remarked on the absence of any macroscopical change in the tonsils. Over a period of many years no clinically recognizable case of tonsillar tuberculosis among children has been observed by us.

Webster (8) found in 86 children with tuberculous cervical adenitis who had had tonsillectomy that 40 or 46.5 per cent had tuberculous lesions of the tonsils. He further states that tuberculous infection of the tonsils rarely advances beyond the microscopical stage and yet, in closely related lymphoid structure, such as the cervical nodes, marked caseation and softening may occur.

Secondary infection of the tonsils in patients suffering from pulmonary tuberculosis is relatively common. Vlasto (9) quotes Strassmann as having found at autopsy tuberculosis of the tonsils in 13 out of 21 patients with advanced pulmonary tuberculosis; he also quotes Dmokowski as having found tuberculous tonsils in a series of 15 autopsies in advanced tuberculosis.

Vlasto further states that according to Mitchell, tuberculosis of the deep cervical lymph nodes develops from a primary focus in the tonsils much more frequently than is supposed; he found that tonsils in these cases show tuberculous lesions in approximately 50 per cent. Likewise, Webster (8) and Macready and Crowe (11) showed that approximately 50 per cent of patients with tuberculous cervical lymphadenitis have lesions in the tonsils. Alpert (10) found palpable cervical nodes in 50 per cent of patients with tuberculous tonsils. Tuberculosis of the tonsils and cervical lymph node tuberculosis are thus intimately connected, as shown by the findings of these investigators as well as many others.

In our group of children the tuberculous lesion in the tonsils was latent and the indications for tonsillectomy are the same as in the non-tuberculous. Two patients in our group had clinical tuberculous cervical adenitis. We believe that removal of the tonsils in these children will reduce absorption from tuberculous foci and perhaps offer a prophylactic measure against the development of tuberculous cervical adenitis.

The route by which the tubercle bacilli reach the tonsils has been the subject of much controversy. Rössner (12) has distinguished between primary and secondary infection. In the former the infection is by the exogenous route, either from inhalation or ingestion; in the latter it is via the endogenous route, either haematogenous or from tuberculous sputum, or by retrograde lymphatic drainage from tuberculous cervical adenitis. Because of the high percentage of positive tonsils in advanced pulmonary tuberculosis, many believe that the sputum is the source of the tonsillar infection. There are ardent adherents for and against this view. We purposely do not elaborate on the different theories, as we feel sufficient evidence has not been brought forth from either side to prove definitely the mode of infection.

It is known that patients who have never had any sputum have microscopical tuberculous tonsils; also, it is known that patients with far advanced pulmonary lesions show a high frequency of positive tonsils microscopically. Long (13) believes that probably all cases of pulmonary tuberculosis have tuberculous tonsils. If sputum alone were the cause of this lesion one would expect clinical tonsillar tuberculosis to be more frequent in the far advanced pulmonary cases, especially in patients who have had large quantities of sputum over a period of years, and yet, clinical tuberculosis of the tonsils is exceedingly rare.

Since this study has shown that 18 of the 19 patients with tuberculosis

of the tonsils had tubercle bacilli in the gastric contents as proved by guinea pig inoculation, we feel that a definite relationship exists between the two conditions. We venture to suggest that these children who harbor the organism in the stomach have unconsciously coughed up and then swallowed the sputum. As to the portal of entry to the tonsil one feels that the mechanism of infection remains unproved, agreeing thus with Long and his coworkers (13) regarding the mode of tonsillar infection in pulmonary tuberculosis.

SUMMARY

The incidence of tuberculosis of the tonsils among 103 female tuberculous children was found by microscopical examination to be approximately 18 per cent. The tuberculous process in the tonsils was latent; there was no macroscopical change in the tonsils that made a clinical diagnosis of the condition possible. Of the 19 patients with tonsillar tuberculosis, 18 had tubercle bacilli in the gastric contents as revealed by guinea pig inoculation. No theory as to the exact mechanism of tonsillar infection in these patients is offered, but a decided relationship between tuberculous tonsils and positive gastric contents as revealed by guinea pig inoculation is pointed out. We feel that these findings are of sufficient interest to report, hoping that others working in this field may be able to elucidate further these results.

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TREATMENT WITH SOLGANAL-B OLEOSUM[1]

A Contribution to the Question of Gold Therapy

FRANK SELIGSON

This paper deals with the treatment of tuberculosis with a gold preparation put out by the Schering Corporation, Bloomfield, New Jersey, which, so far, has not been used on a large scale in this country. It is *Solganal-B Oleosum*. Extensive experiments with Sanocrysin over a period of years have led to inconclusive results and the majority of physicians have abandoned this preparation, in order to avoid the complications connected with its use. *Solganal-B Oleosum* is a gold preparation of a different type. It belongs to the organic gold compounds and is an aurothioglucose compound. It has been used on a wide scale in Europe and the favorable results achieved there, by others as well as by the author of this paper, led to a trial of this preparation at the New Hampshire State Sanatorium. *Solganal-B Oleosum* has shown itself to be less toxic than Sanocrysin, as proved almost unanimously by the results obtained. Its therapeutic index, according to Ehrlich, amounts to 1:50, compared with 1:4 for Sanocrysin. The therapeutic index was defined by Ehrlich as the relation between the smallest healing and the largest tolerable dose.

DOSAGE

As in other types of stimulative therapy, the definite amount of gold to be given in a certain case cannot be predetermined. *Solganal-B Oleosum* lends itself more easily in its administration than other gold preparations on account of its lesser toxicity. In every case we have been able to finish one course of the treatment once it has been started, unless the progress of the disease itself made its further administration inadvisable. The total amount ran from 5 to 9 g. in one course. At first two small doses of 0.01 g. weekly were given, followed by two doses each of .02, .05, .1 and .2 g. within the same period. Doses 0.3 and 0.4 g. were given only once a week. During menstruation no injections were given due to the physiological changes in the blood picture during this

[1] From the New Hampshire State Sanatorium, Glencliff, New Hampshire.

time. The last and highest dose, .4 g., was repeated as often as necessary, but not to exceed the total amount of 8 or 9 g. If needed, a second course was given and the smaller doses were administered this time only once, if, during the first treatment, the tolerance of the patient had been established.

TOLERANCE TOWARDS SOLGANAL-B OLEOSUM

This preparation has shown itself to be well tolerated, with the exception of the occurrence of slight gold exanthemata. No serious complications have arisen in our cases. Urine tests were made at regular intervals and no damage to the kidneys was found. This distinguishes *Solganal-B Oleosum* decidedly from Sanocrysin, which has, as frequently proven, a tendency to deposit gold, particularly in the kidneys, and leads to anatomical changes which are considered to belong to the nephrotic type.

It certainly has to be kept in mind that other complications might occur. Only recently, Mirick reported a case of agranulocytosis due to Sanocrysin and quotes in his paper one case which followed the administration of *Solganal-B Oleosum*. While not underestimating this possibility, it is felt that this ought not to be any reason to refuse a patient the possible benefit of gold treatment.

If slight exanthemata occurred, cevitamic acid was given. Rarely, itching required the use of one or two injections of calcium gluconate. In no case had the treatment to be interrupted.

INDICATIONS

In conformity with many other authors, I observed that exudative cases answer favorably to the treatment with *Solganal-B Oleosum*. Regardless of the extent, this type of tuberculosis offers the best chances, unless a complete breakdown of resistance renders any success impossible. The presence of cavities up to the diameter of two inches is no contraindication, nor is involvement on both sides or involvement of the larynx. The pathological-anatomical nature of this type of tuberculosis favors regression or even complete absorption of the tuberculous tissue, but it is fully realized that this occurs frequently when patients with such lesions are treated solely by bed-rest. However, most of our cases had been on bed-rest either at the Sanatorium or at other places for various periods without any noticeable effect, and, in addition, the speed of regression, as proved by X-ray films, distinguishes our cases from the

ones treated in the usual way. It is felt that exudative cases which supply a fairly large number of complications under pneumothorax treatment quite frequently fare better under gold treatment. Even if gold treatment does not lead to complete arrest of the disease, it often tips the scales of the biological resistance toward the favorable side. Changes in the X-ray appearance in the sense of better defined foci, disappearance of infiltrations and cavities, dropping of the sedimentation rate, disappearance of cough and sputum, improvement of appetite and gain in weight are considered as favorable indications.

Productive cases frequently give good results also, but the very nature of the anatomical structure of productive tuberculous tissue makes quick changes impossible in this type, and we have to rely more upon symptomatic signs than upon changes revealed by X-ray. In typical fibrotic cases no impressive result can be expected, since scar tissue always remains scar tissue and must be considered as a final stage of possible anatomical development which is not subject to further change.

Recent spreads occurring during pneumothorax treatment, or following thoracoplasty, frequently disappear under gold treatment within a very short period of time and make the use of additional surgical measures unnecessary. Several of our cases were chosen with this idea in mind and answered to the treatment favorably. Tuberculosis of the larynx is no contraindication and can be treated along the usual line.

CONTRAINDICATIONS

Tuberculosis of the intestines and of the kidneys must be considered as definite contraindications. One of our unfavorable results was caused by the presence of intestinal tuberculosis which had not manifested itself when the treatment was started. The reasons for the exclusion of tuberculosis of the kidneys were mentioned above and there is no need for further explanation. Cases of haematogenous origin ought not to be treated with gold. While the average case shows warning signals which make continuation of the treatment inadvisable, haematogenous cases frequently react with an unexpected spread whose localization cannot be guessed in advance and which might lead to a fatal meningitis. However, one of our cases was diagnosed as a chronic haematogenous tuberculosis and still received gold treatment. We felt safe in administering it because the pulmonary alterations were very old and probably were in course of transformation into bronchiectatic tissue. In this case, the presence of a recent ulceration of the larynx called for

the use of *Solganal-B Oleosum* and at least temporary success was achieved.

CASE REPORTS

Exudative Lesions

Eleven cases, all far advanced and, with the exception of one, with cavities have been treated with *Solganal-B Oleosum*. Nine of them have completed one or two courses, whereas two are still under treatment but have shown, within a comparatively short time, so much improvement that they have been included in this survey. Within two months after the treatment was started, all cases showed definite improvement as shown by disappearance of foci on the roentgenogram, reduction in the amount of sputum, gain in weight and disappearance of fever. Two patients belong to the dreaded type of juvenile tuberculosis whose prognosis is usually very poor. In spite of marked improvement, one of the cases required the administration of bilateral pneumothorax. Another received gold treatment because, after institution of a pneumothorax on the left side, a flare-up with excavation in the contralateral mid-lung field occurred. This spread and the cavity disappeared within three months following the use of *Solganal-B Oleosum*. The necessity of administering pneumothorax treatment and the previous performance of thoracoplasty in other cases make it difficult to express the results in the usual statistical way. The very nature of gold treatment and its use as auxiliary, as well as sole treatment, necessitate a discussion in general terms about the changes taking place under treatment. Therefore, it is preferred to publish case histories, with X-ray films of single cases in order to prove the effectiveness of the treatment, rather than to produce statistics of questionable value. Anyone experienced in the treatment of tuberculosis will be able to draw his own conclusions and to form his own opinions. All cases showed a marked drop in sedimentation rate which changed in conformity with the clinical development. Of these 11 exudative cases, only one is actually raising sputum containing tubercle bacilli. Three of them do not raise at all and, even with the help of potassium iodide, no expectoration could be obtained. The urine in all cases remained free of albumen during the whole course of the treatment.

Several cases may illustrate what has been said above.

Case 1: E. G., white, female, age twenty-two, with bilateral, extensive tuberculosis, with cavities in the right apex and left mid-lung field and with positive

sputum. She lost weight in spite of bed-rest. She received 5.9 g. of *Solganal-B Oleosum* within six months. Cavities and sputum disappeared and patient gained in weight. Sedimentation rate dropped from 65/100 to 9/25. Follow-up examination in February, 1940, after discharge, showed negative sputum and excellent condition of the patient. No relapse has occurred (figure 1a; figure 1b).

FIG. 1a

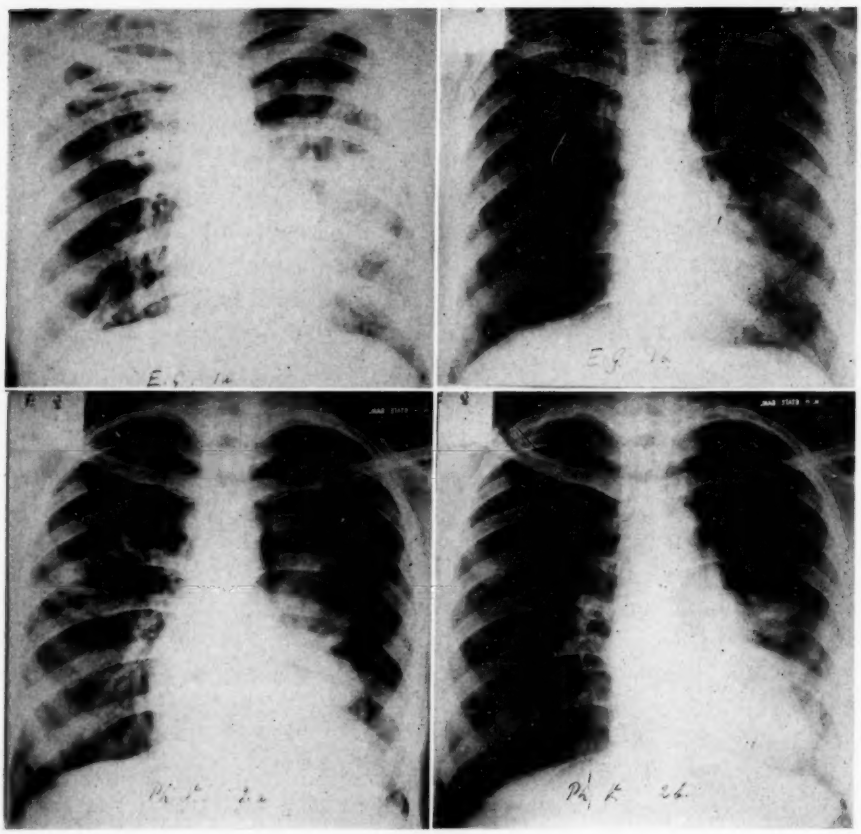

FIG. 1b

FIG. 2a

FIG. 2b

FIGS. 1–2

Case 2: P. V., white, female, Italian descent, age seventeen. On admission, there was multiple cavitation on the left side. She developed a spread with cavity in the right mid-lung field in spite of pneumothorax treatment. She received 9.11 g. *Solganal-B Oleosum* within eight and one-half months. Spread and cavity on the right side disappeared within four months. Sedimentation rate dropped from 76/103 to 30/60. Improvement within the collapsed lung was also noticeable (figure 2a; figure 2b).

Case 3: A. G., white, male, age eighteen with juvenile exudative tuberculosis with cavities in both mid-lung fields (butterfly type). Patient was highly toxaemic. He received 6.09 g. *Solganal-B Oleosum* within six months. Marked clearing on both sides occurred and the cavities disappeared. Shortly after beginning the treatment, patient developed an exudative pleuritis on the left side, which turned into an empyema. The treatment of this led to a temporary pneumothorax, which was partly instrumental in the improvement of the left side. Now, in July, 1940, patient has had a persistently negative sputum for a year. He gained 23 lbs. Sedimentation rate dropped from 57/92 to 4/14 (figure 3a; figure 3b; figure 3c).

Case 4: K. D., white, female, age twenty-nine. She was admitted with caseous pneumonia in the left upper lobe, with cavity beneath the clavicle. In spite of pneumothorax treatment, patient haemorrhaged, the cavity remained open and she developed a spread in the right mid-lung field. Pneumothorax was discontinued and patient placed on treatment with *Solganal-B Oleosum*. A total of 8.3 g. was given within eight months. Marked improvement, disappearance of the cavity and the major part of the infiltration were observed. Her sputum turned negative. Sedimentation rate dropped from 30/58 to 9/24 (figure 4a; figure 4b; figure 4c).

Productive Cases

Four cases of this type have been treated with the average amount of *Solganal-B Oleosum*. After one course, 3 of them were converted. The X-ray films do not show any marked change and, therefore, their publication is considered immaterial. One case remained positive and received the treatment mainly for the purpose of building up resistance for a thoracoplasty which was indicated on the right side. However, during treatment the daily amount of sputum was reduced to almost nothing, and at least a symptomatic improvement was achieved. Patient stood the thoracoplasty well in spite of extensive involvement on both sides.

RELAPSES FOLLOWING TREATMENT

One patient received *Solganal-B Oleosum* on account of a recent infiltration beneath the left clavicle which had reappeared after it had first been absorbed under bed-rest. Within three months the infiltration subsided again. The sedimentation test became normal and the treatment was considered successful. Nevertheless, after several months this infiltration became visible again and another attempt with *Solganal-B Oleosum* was without satisfactory results. In the further course of

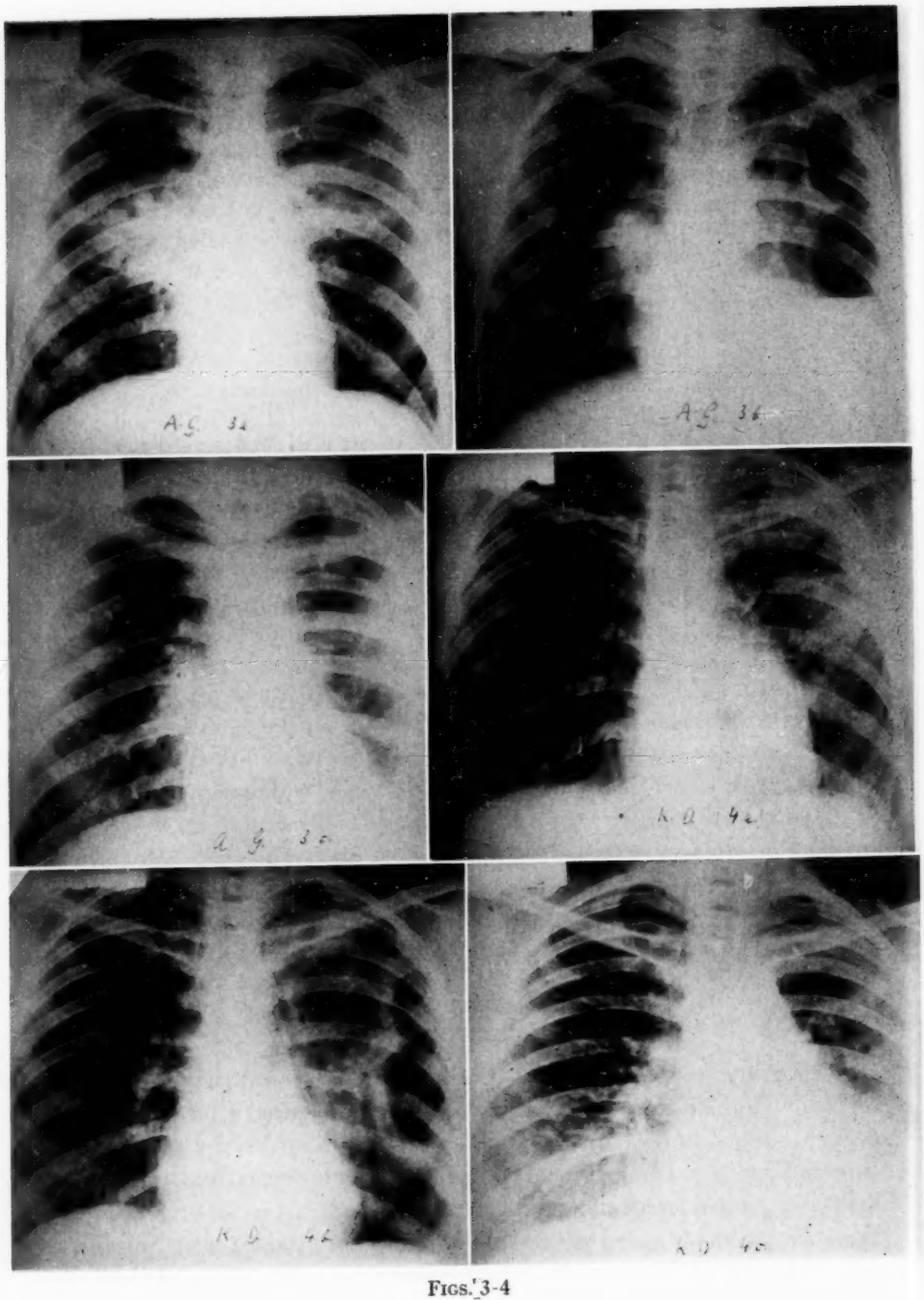

FIG. 3a

FIG. 3c

FIG. 4b

FIGS. 3-4

the disease, the appearance and density of the infiltration changed frequently and the patient eventually underwent a thoracoplasty. Looking back at this case, it is felt that *Solganal-B Oleosum* did not really influence his condition one way or another. In another case which showed marked improvement after a spread of the disease, in spite of bed-rest, a recent infiltration the size of a quarter developed in the right upper lung field. The patient is receiving a second course now which led to disappearance of this infiltration.

UNSUCCESSFUL TREATMENT

One patient with far advanced disease on both sides and intestinal symptoms, which appeared to be the result of toxaemia rather than of an intestinal lesion, was treated but no effect of gold treatment can be stated. The further course of the disease revealed the presence of intestinal tuberculosis and the patient eventually succumbed. Another patient with a recent infiltration on the left side, while having a pneumothorax on the right, was also treated with *Solganal-B Oleosum*. Although this case seemed to be suitable for gold treatment, a large cavity on the left side developed and the treatment was discontinued. A temporary phrenic crushing brought the unfavorable development to a standstill and proved to be more effective in this case than *Solganal-B Oleosum*.

SUMMARY AND CONCLUSIONS

Solganal-B Oleosum is an aurothioglucose compound and distinguishes itself from Sanocrysin which is an inorganic preparation. Its effect is nosotropic and not bacteriotropic. It stimulates the defensive forces of the reticulo-endothelial system.

Solganal-B Oleosum is better tolerated than Sanocrysin. Its toxicity is very low, as proved by the therapeutic index, which is 1:50 for *Solganal-B Oleosum*, compared with 1:4 for Sanocrysin.

The results of the treatment have been gratifying. Even far advanced cases, particularly the ones of the predominantly exudative type, have answered favorably to the administration of *Solganal-B Oleosum*. Cavities and infiltrations disappeared and sputum was converted. Improvement occurred after unsuccessful attempts of treatment with bed-rest and, in some cases also, with artificial pneumothorax. Complications remained within narrow limits.

The author wishes to express his sincere thanks to Dr. Robert M. Deming, Superintendent of the New Hampshire State Sanatorium, for the support extended to him.

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VITAMIN C IN EXPERIMENTAL TUBERCULOSIS[1,2]

M. MAXIM STEINBACH AND SIDNEY J. KLEIN

It is generally recognized that an inadequate amount of vitamin C in the diet causes a lowering of resistance to tuberculosis and other infectious diseases (1, 2, 3, 4, 5, 6). On the other hand, attempts to enhance resistance to tuberculosis by administration of vitamin C have not been conclusive. Leichentritt (7) reported that tuberculous guinea pigs which received large daily supplements of lemon juice developed a more chronic type of tuberculosis and survived longer than controls on a normal diet. Similar observations were made by de Savitch and his collaborators (8). Thaddea and Hoffmeister (9) treated 4 tuberculous guinea pigs with a combination of adrenal cortical hormone and ascorbic acid and found that the treated animals showed less extensive disease than the controls. They also noted that the untreated guinea pigs had very low tissue ascorbic-acid levels, whereas the tissue levels of the treated animals were approximately normal. Birkhaug (10) administered 10 mg. of vitamin C daily to tuberculous guinea pigs, and found that the treated animals had less tuberculosis, more fibrosis and less caseation than the controls.

Stadler and Larisch (11) supplemented a normal diet for tuberculous guinea pigs with daily additions of 5 cc. of lemon juice in one group and $\frac{1}{6}$ tablet of Cebione (8 mg. ascorbic acid) in another. Although the data presented indicated more extensive tuberculosis at autopsy in both treated groups than in the untreated controls, the authors were led to believe that the general condition of the treated animals was better. However, Di Bella (12) claimed that administration of ascorbic acid produced no significant effect on either survival time or extent of the lesions in tuberculous guinea pigs; the latter observation is in agreement with the findings of Heise and Martin (13) and Heise and Steenken (14). Steinbach and Klein (15) reported that daily injection of ascorbic acid increased the tolerance of tuberculous guinea pigs to repeated large

[1] From the Department of Bacteriology, College of Physicians and Surgeons, Columbia University, New York City.

[2] This work was aided in part by a grant from the National Tuberculosis Association.

doses of tuberculin. Of 11 tuberculous guinea pigs treated with ascorbic acid, 10 survived, whereas, of 10 control guinea pigs given similar injections of tuberculin but no ascorbic acid, 9 succumbed to tuberculin shock. In 7 pairs of animals a careful comparative evaluation of the tuberculous involvement was made. In every instance but one, much more extensive tuberculosis was noted in the control guinea pigs than in the treated animals. The average tuberculous involvement for the treated group was rated as 1.8+, as contrasted with 3.4+ for the control group. This observation serves to supplement the earlier report of Bieling (16) that scorbutic tuberculous guinea pigs are more susceptible to tuberculin shock than are nonscorbutic tuberculous controls.

The object of the present experiments was, first, to repeat on a larger scale our previous work relating to tuberculin shock and vitamin C, and second, to study the effects of vitamin C, alone and in conjunction with increasing doses of tuberculin, on the course of acute and chronic experimental tuberculosis.

EXPERIMENTAL METHODS

Tuberculin-negative male guinea pigs were injected into the groin with a weighed amount of bovine pathogenic tubercle bacilli (B1), and placed on a basic diet of timothy hay and oats, with fresh lettuce *ad lib.*, the latter assuring an adequate intake of vitamin C. Weekly weight records were kept throughout the course of the investigation. In all experiments, the animals were divided into four groups. One group received daily injections of tuberculin[3] and of ascorbic acid;[3] the second group was given tuberculin alone; the third group received ascorbic acid alone; the last group remained untreated.

At intervals after infection, one animal from each group was sacrificed; if spontaneous deaths occurred in any group, one animal from each of the other groups was killed, so that a comparative study could be made. The extent of macroscopical tuberculosis was estimated in terms of the number and severity of the lesions in susceptible organs, and was recorded for each organ as from 0 to 4+. These findings were later compared with the results of a microscopical study of sections of the lungs, liver, spleen and lymph nodes. The averages of these values (tables 1 to 3) are only roughly quantitative, but still represent an adequate index of the comparative involvement of the different groups.

[3] The tuberculin used in these experiments was Koch's Old Tuberculin (OT), kindly furnished us by the New York City Department of Health, Bureau of Laboratories. The ascorbic acid used throughout was "Cebione Crystalline Vitamin C," for which we are indebted to Merck and Company.

EXPERIMENTS

1. The effect of combined treatment with ascorbic acid and large doses of tuberculin on tuberculous infection:

Twenty-four albino guinea pigs weighing from 360 to 545 g. were divided into four groups of 6 animals each, of approximately equal range of weight. All animals were infected with 0.001 mg. bovine tubercle bacilli (B1) subcutaneously in the groin. Fifteen days later the guinea pigs were skin-tested with 1 mg. OT and all showed strongly positive reactions. On the twenty-second day after infection the groups were started on their different regimens:

Group 1 (*OT + C*) received injections twice weekly of OT in increasing amounts from 100 to 600 mg., and daily injections of 5 mg. ascorbic acid freshly dissolved in 0.25 cc. sterile distilled water.

Group 2 (*OT*) received subcutaneous injections of OT twice weekly, as in group 1.

Group 3 (*vitamin C*) received daily injections of 5 mg. ascorbic acid, as in group 1.

Group 4 (*controls*) received daily subcutaneous injections of 0.25 cc. sterile water.

The results are presented in table 1. Four of the 6 deaths occurred in the group receiving only tuberculin, while the other 2 deaths occurred in the group receiving tuberculin and ascorbic acid. These results, although in line with our previous findings, were not as striking as before, perhaps because in the present experiment tuberculin was given over a longer period of time (thirteen weeks). Because they lived longer, the animals in both groups showed very extensive disease, and it was not always clear whether the immediate cause of death was due to tuberculin shock or to very advanced tuberculosis. The values given for the average degree of tuberculous involvement show that the animals which had received vitmain C alone or vitamin C with OT had less tuberculosis than either the controls or the animals injected with OT alone. This was true when groups or individual animals were compared in separate autopsy sets. There appeared to be less caseation in ascorbic-acid treated animals than in animals without ascorbic acid, an observation which was subsequently confirmed in two later experiments.

The average increment in the body weight of the guinea pigs in the different groups from day of infection to day of autopsy was as follows: Control group 23 per cent; OT group 16 per cent; OT + C group 5.9 per cent; vitamin C group 44 per cent. Thus the vitamin C group

showed an average weight increase almost double that of the control group, while the two groups receiving tuberculin showed the lowest average weight increases.

TABLE 1

Effect of ascorbic acid and large doses of tuberculin on acute experimental tuberculosis

TUBERCULIN INJECTIONS* SUBCUTANEOUS		I TUBERCULIN AND ASCORBIC ACID		II TUBERCULIN ONLY		III ASCORBIC ACID ONLY		IV NO TREATMENT	
Date	Dosage	K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement
	mg.								
4- 9	100								
4-13	125								
4-16	150								
4-20	175								
4-23	200								
4-27	225								
4-30	250								
5- 4	250								
5- 7	250								
5-11	250	K #1	2+	D #7	4+	K #13	2+	K #19	4+
5-14 to 5-28 (5 times)	250								
6- 1	300	K #2	2+	D #8	4+	K #14	3+	K #20	3+
		K #3	3+	D #9	3+	K #15	3+	K #21	3+
6- 4	300								
6- 8	325	D #4	4+	K #10	3+	K #16	2+	K #22	4+
6-11	375	D #5	3+	K #11	3+	K #17	3+	K #23	4+
6-15	450								
6-18	500								
6-22	600	K #6	3+	D #12	4+	K #18	2+	K #24	3+
Average tuberculous involvement			2.8+		3.5+		2.5+		3.5+

Degree of tuberculous involvement recorded as 0 to 4+. K indicates killed; D indicates died.

Guinea pigs injected subcutaneously with 0.001 mg. B1 (3-5-36). Treatment begun twenty-two days later.

* The indicated schedule of tuberculin dosages was preceded by 4 intracutaneous injections of 100 mg. OT. All deaths occurred within two days after the indicated tuberculin injection.

In order to determine the effect of vitamin C, the excised and sliced adrenals of animals in the first experiment were tested grossly for reducing substances with 0.4 per cent silver nitrate for one-half hour

(17) and the cortex was examined for visible blackening. Five of the 6 animals in each of the vitamin-C and OT + C groups showed strong reactions, whereas the control group and the OT group each showed only one instance of a definite reaction. Ascorbic-acid administration had therefore served to maintain a higher vitamin C level.

2. The effect of combined treatment with ascorbic acid and small doses of tuberculin on tuberculous infection: In view of the fact that the first experiment had suggested some mitigation of the toxic effects of large doses of tuberculin by ascorbic acid, it seemed of interest to reinvestigate the value of this substance for desensitization in tuberculosis. Within recent years, several investigators (18, 19, 20) have expressed an opinion that allergy may be a harmful factor in tuberculosis, and have therefore suggested desensitization by means of tuberculin. The chief obstacle to all such experiments has been the difficulty of obtaining complete desensitization unless very large doses of tuberculin are used. In an effort to prevent the toxic effects of such large doses, tuberculin in small, gradually increasing doses, combined with vitamin C, was given in the second experiment.

Twenty-eight albino guinea pigs, 400 to 450 g. in weight, were infected with 0.000,1 mg. bovine tubercle bacilli (B1) subcutaneously in the groin. Three weeks later all guinea pigs gave a positive skin reaction to 0.1 mg. tuberculin. The guinea pigs were then divided into four groups of 7 animals each, and treatment by the subcutaneous route was begun twenty-six days after infection.

Group 1 (*OT + C*) received injections twice weekly of OT in increasing doses, and daily administration of 5 mg. ascorbic acid.

Group 2 (*OT*) received injections twice weekly of OT in increasing doses.

Group 3 (*vitamin C*) received daily injections of 5 mg. ascorbic acid.

Group 4 (*controls*) received daily injections of 0.25 cc. of saline. The schedule of tuberculin doses was as follows: starting with 0.1 mg. OT, the dose was doubled in each succeeding injection until 6.4 mg. was reached; the next dose was 10 mg.; thereafter the dosage was increased at the rate of 10 per cent. At the conclusion of the experiment four months later, the last dose was 110 mg. The tuberculin was used in such dilution that the volume injected was usually less than 0.5 cc. The tuberculin skin sensitivity of the control group (4) and the vitamin-C group (3) was tested fifty-six days after infection. Comparison of the reactions to test doses of 0.1, 0.01, and 0.001 mg. of OT showed no marked difference between the two groups, although in the C-treated animals the reacting area was smaller and less intense. No significant difference in growth was noted between the various groups.

As shown in table 2, most of the animals presented very advanced generalized tuberculosis. Only the OT + C group gave some evidence of retardation of the disease. This group showed less tuberculosis than the controls in 5 of 7 instances, and in 4 autopsy sets showed distinctly less marked disease than any of the other animals. The OT group and the vitamin-C group showed no significant difference from the controls. The small doses of OT used in this experiment apparently did not influence the disease. The results in the vitamin-C group are at variance

TABLE 2

Effect of ascorbic acid and moderate doses of tuberculin on acute tuberculosis

DURATION OF INFECTION	FINAL DOSE OF TUBERCULIN*	I TUBERCULIN AND ASCORBIC ACID		II TUBERCULIN ONLY		III ASCORBIC ACID ONLY		IV NO TREATMENT	
		K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement	K or D and guinea pig number	General estimate of involvement
days	*mg.*								
94	33	K #25	2+	D #32	4+	K #39	3+	K #46	4+
102	39	K #26	3+	K #33	4+	K #40	4+	K #47	3+
108	47	K #27	3+	K #34	3+	D #41	4+	K #48	4+
111	52	K #28	2+	K #35	2+	K #42	4+	D #49	3+
112	52	D #29	2+	K #36	4+	K #43	3+	K #50	4+
134	92	D #30	3+	K #37	4+	K #44	4+	K #51	4+
143	111	K #31	3+	K #38	4+	K #45	4+	D #52	4+
Average tuberculous involvement.....			2.5+		3.5+		3.7+		3.7+

Degree of tuberculous involvement recorded as 0 to 4+. K indicates killed; D indicates died.

Guinea pigs injected subcutaneously with 0.000,1 mg. B1. Treatment begun twenty-six days later.

* Indicates maximum final dose of tuberculin received by 2 of the guinea pigs in each autopsy set.

with those obtained in previous experiments, where ascorbic acid appeared to be of therapeutic value during the initial stages of the disease. The difference may depend in part on the prolonged duration of the present experiment, in which some of the animals were permitted to live for five months. There were indications of fibrosis in 13 of the 14 animals treated with the vitamin; but in the non-vitamin-treated guinea pigs, only 6 of the 14 showed slight fibrosis.

3. The effect of combined tuberculin and ascorbic-acid treatment in

chronic tuberculosis: In view of our findings that treatment with tuberculin and vitamin C may be beneficial, it seemed possible that an even greater effect might be obtained by applying this mode of treatment to a low-grade, chronic form of tuberculous infection. Animals were therefore vaccinated with a nonpathogenic strain of tubercle bacilli and subsequently reinfected with virulent organisms.

Thirty-five non-albino guinea pigs were injected subcutaneously with 0.1 mg. R1 (a human nonpathogenic strain) in the right groin. Thirty days later, when the animals were found to have become sensitive to OT, they were reinfected with virulent bovine tubercle bacilli (B1). The animals were then divided into four groups and treatment was begun one week following reinfection. All injections were made subcutaneously.

Group 1 (OT + 5 mg. C) received twice weekly injections of OT in increasing doses, also daily injections of 5 mg. ascorbic acid.

Group 2 (OT) received the same OT treatment as group 1.

Group 3 (vitamin C) was given either 5 or 10 mg. of ascorbic acid daily.

Group 4 (controls) received 0.25 cc. sterile saline daily.

The schedule of tuberculin doses was as follows: starting with 0.01 mg., the dose was doubled in each succeeding injection until 10 mg. was reached. The amount of tuberculin was then increased by 10 per cent in each succeeding injection. After seven months a dose of 1,000 mg. was reached. This dose was maintained during the final 10 injections.

The results of this experiment, summarized in table 3, showed more striking group differences than those obtained in previous experiments. Both the OT +C group and that treated with vitamin C alone presented significantly lower average involvement than the control group. Three guinea pigs in the OT +C group and 3 in the vitamin-C group showed less disease than any other animals in the entire series. The OT group also gave some evidence of having been favorably affected by treatment, but only the OT +C group was consistently better than any of the other groups. Twelve of the C-treated guinea pigs showed some fibrosis, whereas only 2 of the 11 non-vitamin animals showed this effect.

All animals showed a gain in weight during the course of the slowly progressing infection. The average increase for the various groups from the date of reinfection to the date of autopsy was: controls, 33 per cent; OT, 32 per cent; OT +C (5 mg.), 43 per cent; 5 mg. C, 39 per cent; 10 mg. C, 39 per cent. Although the OT +C group showed the highest average weight increase, it is doubtful whether this difference is significant.

In two of the autopsy sets in the last experiment, the adrenals and livers were assayed for reduced ascorbic acid by titration with 2:6 dichlorobenzenone indophenol (Eastman Kodak P3463), according to the method of Musulin and King (21). The tissues of two noninfected guinea pigs were assayed at the same time for purpose of control. Intake of vitamin C from any source was excluded for twenty-four hours before the assays. The average adrenal ascorbic-acid values in milligrams per gram were as follows: group 1 (OT + 5 mg. C), 0.67; group 2

TABLE 3

Effect of ascorbic acid and moderate doses of tuberculin on chronic tuberculosis

DAYS SINCE REINFECTION	FINAL DOSE OF TUBERCULIN*	GROUP I TUBERCULIN + ASCORBIC ACID (5 MG.)		GROUP II TUBERCULIN		GROUP III				GROUP IV NO TREATMENT	
						Ascorbic acid 5 mg.		Ascorbic acid 10 mg.			
		Guinea pig number	General estimate of involvement	Guinea pig number	General estimate of involvement	Guinea pig number	General estimate of involvement	Guinea pig number	General estimate of involvement	Guinea pig number	General estimate of involvement
	mg.										
62	16	53	1+	59	2+	64	1+	70	1+	77	4+
78	26	54	1+	60	1+	65	1+	71	1+	78	2+
105	57	55	0	61	1+	66	1+	72	1+	79	2+
202	678	56	1+	62	4+	67	1+	73	2+	80	2+
228	1000	57	1+			68	1+	74	1+	81	1+
246	1000	58	2+	63	2+	69	3+	75	1+	82	4+
								76	4+		
Average tuberculous involvement.....			1+		2+		1.3+		1.8+		2.5+

Degree of tuberculous involvement recorded as 0 to 4+.

Guinea pigs sensitized with 0.1 mg. R1 subcutaneously; reinfected with 0.01 mg. B1 subcutaneously.

Treatment begun one week after reinfection.

* Indicates maximum final dose of tuberculin received by 2 of the guinea pigs in each autopsy set.

(OT), 0.23; group 3 (5 mg. C), 0.56, (10 mg. C) 1.0; group 4 (tuberculous controls), 0.27; normal nontuberculous control group, 0.53. The ascorbic-acid values, in the liver, in general, paralleled very closely the ascorbic-acid values in the adrenal. There seemed to be close agreement with the amount of ascorbic acid injected. Thus, the highest values were obtained in the 10 mg. C group, the next highest adrenal ascorbic-acid values being found in the groups receiving 5 mg. ascorbic acid, with or without tuberculin. The lowest values were encountered in the

Liver Ascorbic Acid
Adrenal Ascorbic Acid

tuberculous control group and in the OT group. It would therefore appear that the tuberculous guinea pig, despite consumption of large amounts of lettuce, possesses a low tissue ascorbic-acid level, and that this level is raised significantly by injection of 5 mg. or more of ascorbic acid daily.

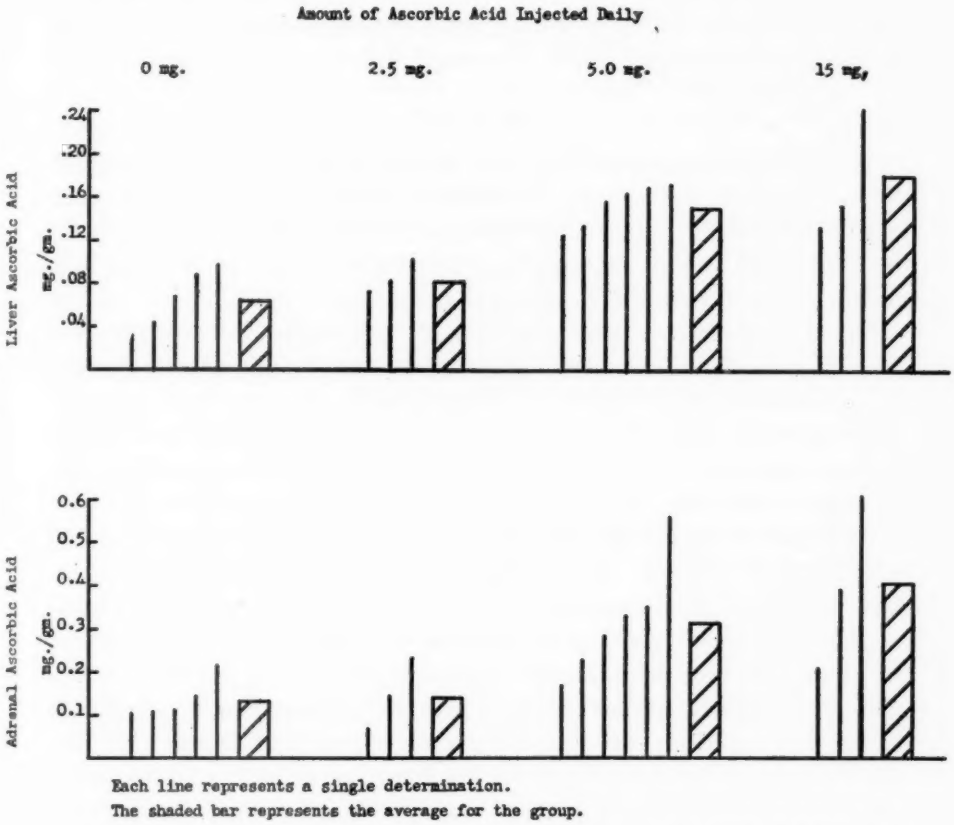

CHART 1. Tissue ascorbic-acid levels in tuberculous guinea pigs which died following tuberculin injection.

A further demonstration of the decreased tissue levels of vitamin C in experimental tuberculosis was obtained in another experiment, in which ascorbic-acid assays were made of the tissues of 17 tuberculous guinea pigs which died following injection twice weekly of increasingly large doses of tuberculin over a period of about one month. Daily injections of 2.5, 5 or 15 mg. of ascorbic acid had been given in separate

groups, and a control group had received similar injections of tuberculin, but no ascorbic acid. All but one of the guinea pigs in the 5 mg. and 15 mg. C groups gave values for adrenal ascorbic acid greater than 0.2 mg./gm., while 6 of the 8 animals in the control and 2.5 mg. C groups gave values below 0.2 mg./gm. As indicated in chart 1, the average values for the adrenal ascorbic acid were: control group, 0.14 mg./gm.; 2.5 mg. C group, 0.14 mg./gm.; 5 mg. C group, 0.32 mg./gm.; 15 mg. C group, 0.41 mg./gm.

DISCUSSION

When tuberculous guinea pigs were subjected to a regimen of repeated toxic doses of tuberculin, 13 of a total of 16 animals (81 per cent) died of tuberculin shock. In another group of tuberculous guinea pigs which, in addition to tuberculin, had been treated with ascorbic acid, only 3 deaths occurred among 17 animals (18 per cent).

Tuberculous guinea pigs injected with tuberculin and ascorbic acid showed less tuberculous involvement than did the untreated controls. This favorable result was not to be attributed solely to amelioration of the cumulative toxic effects of successive tuberculin injections, for some disease-retarding effect was observed with ascorbic acid in parallel groups in which tuberculin injections had been omitted.

Tuberculous guinea pigs repeatedly injected with large doses of tuberculin showed very low titration values for tissue ascorbic acid, despite consumption of large amounts of lettuce. Apparently such animals have a greatly increased demand for vitamin C. Daily injection of from 5 to 15 mg. ascorbic acid caused a considerable increase in the ascorbic-acid levels in these guinea pigs. Tuberculous guinea pigs not receiving tuberculin injections also showed greatly diminished tissue ascorbic-acid levels. Daily administration of 10 mg. of ascorbic acid again restored the tissue vitamin levels to values within the range reported for noninfected guinea pigs on a similar dietary regimen. These findings suggest that ascorbic acid favorably affects the course of tuberculosis and intoxication by tuberculin by meeting the increased demand for the vitamin which is manifested under these conditions.

Combined tuberculin and ascorbic-acid therapy did not prove superior to vitamin therapy alone when tuberculin was used in repeated large toxic doses. However, beneficial results were obtained with ascorbic acid combined with tuberculin given in small, gradually increasing doses. Thus, although prolonged treatment with moderate doses of either

tuberculin or ascorbic acid had little effect on the progress of disease, combined administration of both substances resulted in distinct mitigation of the infectious process.

In guinea pigs suffering from chronic, slowly progressive tuberculosis, some beneficial effects were obtained by the administration of either tuberculin or ascorbic acid alone. However, a combination of ascorbic acid and tuberculin treatment gave distinctly better results.

These results suggest the use of ascorbic acid in conjunction with tuberculin in attempts at therapeutic desensitization. The ascorbic acid would seem to lessen the danger of toxic episodes which so often accompany tuberculin treatment in man. This concept is further supported by our observation that vitamin-C treated animals reacted less severely to intracutaneous doses of tuberculin. Our experiments on ascorbic-acid therapy in human tuberculosis were quoted by Wright (3), in 1936, and will be reported in detail elsewhere.

Our observation that ascorbic acid possesses some therapeutic value in experimental tuberculosis and serves to minimize tuberculin intoxication complements the anti-infectious and antitoxic properties of the vitamin reported in other infectious diseases. It would seem, however, that vitamin C were better regarded as a useful adjuvant in the treatment of tuberculosis than as a specific therapeutic agent. Although it has been amply demonstrated that vitamin-C deficiency makes for diminished resistance in this disease, the effect of the vitamin in arresting the morbid changes of an already progressed tuberculous process is probably very limited. What therapeutic value it possesses in man is still in question, but restoration of deficient vitamin-C concentrations to normal levels would undoubtedly be a desirable objective to accomplish in the treatment of the disease.

CONCLUSIONS

Daily injections of crystalline vitamin C into tuberculous guinea pigs raised the tissue levels of ascorbic acid. This treatment appeared to increase the tolerance to repeated large doses of tuberculin and to retard the progress of tuberculosis. Fibrosis was more prevalent and caseation less marked in animals that received vitamin C. Combined administration of tuberculin and ascorbic acid gave better results than the use of either substance alone. More favorable results were obtained in the chronic than in the acute form of tuberculosis. The use in man of ascorbic acid in conjunction with tuberculin is suggested to minimize the toxic effect of the latter substance.

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THE EFFECT OF VITAMIN C ON EXPERIMENTAL TUBERCULOSIS IN THE RABBIT[1,2]

M. MAXIM STEINBACH, S. J. KLEIN AND C. J. DUCA

Many workers have studied the effect of vitamin-C deficiency on infectious diseases and, in the main, have experimented on the guinea pig, which is highly susceptible to scurvy. In previous reports, Steinbach and Klein have shown the importance of maintaining the vitamin-C level in the tuberculous guinea pig. It seemed of interest to repeat this work, using the rabbit which does not develop scurvy on a deficient diet, as it is able to synthesize its own vitamin C. The objects of these experiments were, first, to determine whether the vitamin-C level is lowered in the tuberculous rabbit as in the guinea pig, and, second, to observe the effect of the administration of vitamin C, and of tuberculin, either alone or together, on the course of the disease.

METHODS

Seventeen tuberculin-negative Dutch rabbits, eight weeks old, were divided into four groups and treated as follows:

Group I. Controls: 0.2 cc. saline injected subcutaneously, starting the day before infection and continued daily.

Group II. OT: as soon as animals were allergic, treatment was begun with a skin-test dose of tuberculin, and this was doubled at each succeeding injection until 20 mg. was reached, after which the doses were increased by 10 per cent at each injection.

Group III. OT + C: treated with tuberculin twice weekly, as group II, plus daily administration of 10 mg. vitamin C in 0.2 cc. distilled water.

Group IV. C: daily subcutaneous injections of 10 mg. vitamin C in 0.2 cc. distilled water, started the day before infection.

All rabbits were infected intravenously with pathogenic bovine tubercle bacilli (B1), half of each group receiving 0.000,1 mg., while the other half received 0.001 mg. The weights of the animals were recorded weekly. At intervals after infection, an animal from each group was sacrificed, and the

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[2] This work was aided, in part, by a grant from the National Tuberculosis Association.

extent of tuberculosis in the susceptible organs was estimated. All autopsy findings were confirmed by microscopical examination of sections from representative organs.

The organs involved were mainly the lungs and kidneys. The tubercles were either single or conglomerate, and were chiefly of epithelioid type with central areas of caseation. The averages of the findings provide a comparison of the amount of tuberculosis in the different groups. The adrenals of the animals which had been infected with the larger dose of tubercle bacilli were titrated for their content of reduced ascorbic acid. The results are shown in table 1.

As can be seen from the findings presented in table 1, no essential differences were found in the severity of tuberculosis between the four

TABLE 1

GROUP	NUMBER OF RABBITS	INFECTING DOSE	DAYS OF LIFE AFTER INFECTION	AVERAGE INVOLVEMENT	WEIGHT CHANGES	ADRENAL VITAMIN C	NUMBER OF RABBITS	INFECTING DOSE	DAYS OF LIFE AFTER INFECTION	AVERAGE INVOLVEMENT	WEIGHT CHANGES
		mg.				*mg./gm.*		*mg.*			
I	3	0.001	115	2+	+475	1.82	2	0.0001	174 276	2.3+	+1,118
II	2	0.001	115	3+	+520	1.76	2	0.0001	174 276	2+	+1,180
III	2	0.001	115	2.5+	+780	2.52	2	0.0001	174 276	2.5+	+1,125
IV	3	0.001	115	2+	+680	1.87	1	0.0001	276	4+	+950

groups, irrespective of the size of the infecting dose of tubercle bacilli. There were no striking differences in weight changes, except for a slight increase in groups III and IV. Group III which had received both tuberculin and vitamin C showed a somewhat higher vitamin-C content in the adrenals than any of the other groups. The average vitamin-C level in the adrenals of two normal litter-mate rabbits of the same age as the experimental animals was 1.79 mg./gm. tissue. It should be noted that the animals infected with the smaller dose of tubercle bacilli were allowed to live over twice as long as the others.

SUMMARY

Experimental tuberculosis in the rabbit, unlike that in the guinea pig, is not influenced by the administration of vitamin C, even though this procedure causes a 50 per cent increase in the ascorbic-acid content of

the adrenals. Nor does the disease in the rabbit lower vitamin-C levels below normal, as has been shown in the guinea pig.

CONCLUSION

The vitamin-C metabolism of an animal, such as the rabbit, that synthesizes its own ascorbic acid, is not readily disturbed by tuberculous infection or intoxication, nor is the course of experimental tuberculosis in such an animal affected by the administration of vitamin C or of vitamin C combined with tuberculin.

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HUMAN TUBERCULOSIS IN A BOVINE[1]

Case Report of a Spontaneous Infection in an Adult Bovine

WILLIAM H. FELDMAN AND HAROLD MOSES

The susceptibility of cattle to *Mycobacterium tuberculosis* other than variety *bovis* is negligible. The avian variety is capable of infecting cattle to a limited degree and a moderate number of cases in which cattle have been infected with avian tubercle bacilli have been reported (1). Reported instances in which the human variety of the tubercle bacillus was demonstrated as the infective agent in bovine tuberculosis are few indeed. The paucity of reported cases of this character would seem to justify a description of such a case.

REPORT OF A CASE

Source of material: In compliance with a request for bovine tissue containing lesions of tuberculosis, there was received in January, 1940, from Dr. D. D. Tierney, Inspector in Charge, Federal Meat Inspectors Service, South St. Paul, Minnesota, tissues from the carcass of an adult bovine animal that had been condemned on postmortem inspection on account of tuberculosis. The lesions observed at necropsy consisted of well marked lesions of a caseo-calcareous character in one of the bronchial lymph nodes, a small calcified lesion in the lung and a slight calcified lesion in one of the mesenteric lymph nodes. The tissues were transported to the laboratory in dry borax.

After the character of the tuberculous infection had been ascertained by laboratory procedures, attempts were made to trace the origin of the animal from which the lesions had been obtained. Investigation revealed that the animal in question was one of a group of 95 that had been imported from Canada. The group had been made up of smaller lots and information as to the original ownership of this particular animal was not available.

Methods: At the laboratory the tissues were immersed for eight to ten seconds in boiling water for the purpose of removing the borax and to decrease the possibility of extraneous contamination. The lesions from the lung and from the bronchial lymph node were selected for subsequent study.[2] A small portion of each lesion was removed and fixed in neutral formalin solution.

[1] From The Mayo Foundation, Rochester, Minnesota.

[2] It should be mentioned that the reason for obtaining these tissues was for the purpose of isolating a "fresh" strain of bovine tubercle bacilli to be used in another study.

Subsequently sections for histological study were prepared. The rest of the tissue representing the respective lesions was suspended separately for the isolation and growth of tubercle bacilli.

Culture: The procedures followed were those described elsewhere (2). They consisted essentially of treating portions of the suspended specimens with 5 per cent oxalic acid and, after centrifugation, seeding the precipitate over the surface of egg-yolk agar and glycerinated egg-yolk-agar slants. The inoculated slants were sealed with latex-tissue finger-cots and incubated at 37.5°C. The slants were examined weekly for evidence of growth.

After fifty-five days of incubation each of the slants contained a few to a moderate number of small discrete colonies composed of acid-fast bacillary forms. The colonies were rather dry and were inclined to stick to the medium. Of especial interest was the fact that colonies had occurred on the glycerinated medium. In some instances the colonies were larger and more numerous on the medium containing glycerin than on the medium without glycerin. Since the physical characters of the colonies were distinctly different from those of colonies of typical avian tubercle bacilli, it was likely that the colonies represented a mammalian strain of *Mycobacterium tuberculosis*. Furthermore, the fact that the bacteria were definitely glycerophilic, while freshly isolated strains of bovine tubercle bacilli usually are not, suggested the possibility that the colonies represented tubercle bacilli of the human type.

That the bacillary type of the bacterium might be determined, additional studies were done. Transfers were made to glycerinated and nonglycerinated media and it was noted that the glycerinated medium yielded the most luxuriant growth. Also, the resultant growths had the dry, crumbly characteristics of the human type of tubercle bacilli.

Animal inoculations: To determine the pathogenicity of the strain each of two guinea pigs, two rabbits and two chickens was inoculated with 0.001 mg. of a forty-nine-day-old culture.[3] The guinea pigs were inoculated subcutaneously and the rabbits and chickens, intravenously.

The bacteria injected proved to be pathogenic for the two guinea pigs but not for the rabbits or the chickens. The failure of the bacteria to produce a malignant or progressive tuberculosis in rabbits provides impressive evidence to support the belief that the organisms were not bovine tubercle bacilli and the resistance exhibited by the chickens makes it equally evident that the bacteria were not avian tubercle bacilli.

The data assembled would seem to indicate that the organisms obtained from the lesions of the bovine animal were tubercle bacilli of the human type. The ability of the strain when first isolated to prosper on the glycerinated medium, its dry, crumbly appearance and its pathogenicity for guinea pigs

[3] The chickens had previously been subjected to a tuberculin test and had failed to react.

but not for rabbits and chickens appear to be sufficient proof to justify this conclusion.

Histopathology of bovine lesions: Duplicate sections were prepared of the respective lesions. One was stained with haematoxylin and eosin and the

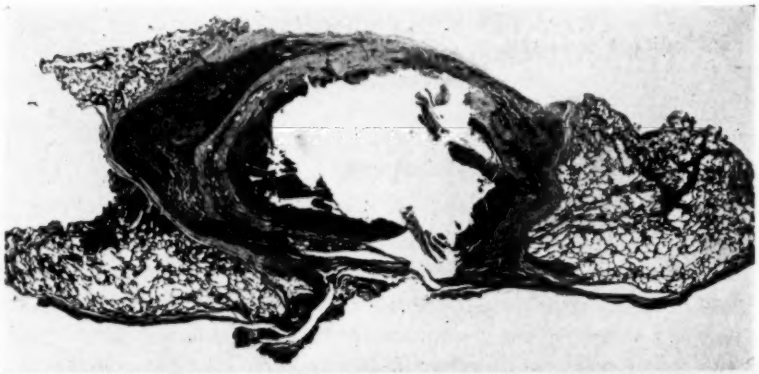

FIG. 1

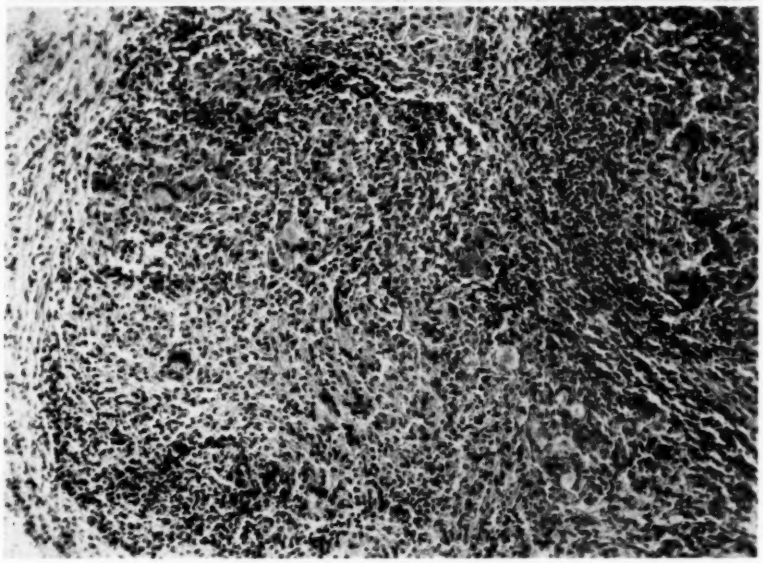

FIG. 2

FIG. 1. Encapsulated tuberculous nodule in the parenchyma of the lung. The caseocalcareous central portion was lost during the preparation of the histological section (×8).

FIG. 2. Portion of conglomerate tubercle, bronchial lymph node (×110).

other with a haematoxylin-carbolfuchsin combination. The lesion in the lung consisted essentially of a heavily encapsulated focus of caseation with a minimal deposit of mineral salts (figure 1). Superimposed, peripherally, between the central area of caseation and the fibrous connective tissue capsule

was a rather broad, highly cellular zone consisting mostly of histiocytic-epithelioid elements and a few lymphocytes. A definite transition of the more peripheral histiocytic elements to fibroblasts was apparent. The earlier expansion of the lesions had caused an encroachment on much of the adjacent parenchymal tissue of the lung, and atelectasis had resulted. The connective tissue elements of the capsule showed hyalinizing tendencies. Giant cells of the Langhans type were not seen nor were acid-fast bacillary forms found. Taken as a whole, the lesions in the lung appeared to represent a process that had lost its momentum and further appreciable progression seemed unlikely. However, that the lesion was a potential hazard must be recognized since viable tubercle bacilli were demonstrated by culture.

The bronchial lymph node was extensively involved. Except for a narrow peripheral zone the lymphoid elements had been largely replaced by the tuberculous process. The latter was characterized by the occurrence of innumerable multiple or conglomerate tubercles and the presence of an excessive number of giant cells of the Langhans type (figure 2). The majority of the tubercles were epithelioid with little if any detectable necrosis. In the material studied only one small area of caseation necrosis was observed. In the tissue débris a few acid-fast bacillary forms were seen. The structural similarity of the tubercles throughout the lymph node was indicative of an infection of multicentric origin; all seemed to have existed for approximately the same duration.

The dissimilarity of the structure of the lesions in the lung and those in the bronchial lymph node was striking and perhaps significant. Considered together, the lesions in the two situations are quite comparable to those that characterize the primary infection of the lungs in children, which is commonly designated as the primary complex. This type of tuberculous infection is usually characterized by a single parenchymal lesion that commonly encapsulates and undergoes caseocalcareous retrogression, with secondary involvement of the hilar or bronchial lymph nodes. Occasionally the lesions progress and lymphatic and haematogenous dissemination of the disease may occur.

Whether or not the fact that human and not bovine tubercle bacilli were responsible for the lesions in the bovine accounts for the rather distinctive character of the morbid changes is problematic but worthy of consideration.

COMMENT

Since the time of Koch (12) the relation of bovine tuberculosis to tuberculosis in human beings has received much attention from various investigators with the result that there is no longer any doubt about the infectiveness of bovine tubercle bacilli for human beings. It is also generally accepted that human tubercle bacilli have but limited pathogenicity for cattle. Koch was among the first to come to this conclusion,

basing his opinion on the failure of 19 young cattle to become infected after a rather formidable exposure to tuberculous sputum. However, although Koch's experiment yielded negative results, others, including Fibiger and Jensen (13, 14) and Griffith (15), succeeded in demonstrating that cattle, especially calves, could be infected with human tubercle bacilli.

Cases in which human tubercle bacilli have been demonstrated in naturally infected cattle are few. Of the 9 cases reviewed, 4 were in calves, 2 were in heifers and 3 were in cows. The salient features of the 9 cases, as reported by the respective workers are given in table 1.

The evidence available suggests that human tubercle bacilli are rarely responsible for lesions of naturally acquired tuberculosis of cattle. The infrequency of this type of infection and the character and anatomical distribution of the morbid changes make it unlikely that the human type of tuberculous infection in cattle may be transmitted from one animal to another. In other words, once the disease is established in a bovine animal, it usually remains localized with the lesions showing a marked tendency to heal or to become quiescent.

There is, however, a phase of the problem that is worthy of brief comment. This is the possibility of cattle becoming sensitized to mammalian tuberculin as a consequence of contact with human tubercle bacilli derived from persons affected with pulmonary tuberculosis. Stenius (5), Plum (16), Bang and Jepsen (7) and Nielsen and Plum (17) have investigated this problem and have assembled a sufficient amount of presumptive evidence to substantiate the conclusions that cattle, exposed to infective material from human beings affected with human tubercle bacilli, may become sufficiently sensitized to mammalian tuberculin to elicit a diagnostic reaction to the intracutaneous tuberculin test. The reports reviewed seem to indicate that after the source of the human tubercle bacilli has been removed, the animals gradually lose their sensitivity to tuberculin. It is obvious, therefore, that persons with active pulmonary tuberculosis should be excluded from premises frequented by cattle—not especially because the disease may be transmitted to the cattle but because of the greater possibility of sensitizing the animals to tuberculin that may be used in subsequent diagnostic tests.

The question of whether or not a cow harboring human tubercle bacilli as a consequence of natural exposure will eliminate tubercle bacilli with the milk has been studied rather comprehensively by Hinderson

(18) and by Nielsen and Plum (17) and the results failed to reveal a single instance in which this occurred.

TABLE 1

Previously reported cases in which tubercle bacilli of the human type have been demonstrated in naturally infected cattle

AGE OF ANIMAL	EXPOSURE TO PULMONARY TUBERCULOSIS IN A HUMAN BEING	REACTION OF ANIMAL TO MAMMALIAN TUBERCULIN	LESIONS OF TUBERCULOSIS IN ANIMAL	REPORTED BY
4 months	Yes (suspect)	Yes	Small caseocalcareous nodule with smaller peripheral nodules in one mesenteric lymph node	Giltner (3)
Cow	Not stated	Not stated	Gross lesions in bronchial and mediastinal lymph nodes	Hibma (4) (quoted by Plum)
Calf	Yes	*	Gross lesions not found	Stenius (5)
Calf	Not stated	Not stated	Few subpleural foci of one lung. Involvement of one mediastinal lymph node	Griffith (6)
Calf	Yes ("open" tuberculosis)	†	Caseous lesion in left bronchial lymph node	Bang and Jepsen (7)
Cow	Probable	Yes	Lesion in left bronchial lymph node	Van der Schaaf and van Zweiten (8)
15 months	Not ascertained	Yes	Human tubercle bacilli obtained from composite suspension prepared from parotid, pharyngeal and submaxillary lymph nodes	Reid (9)
Cow	Not stated	Not stated	Lesion in retropharyngeal lymph node	Watson (10) (quoted by Nielsen and Plum)
Heifer	Yes‡	Yes	Small caseocalcareous nodule in a mesenteric lymph node	Nielsen and Plum (11)

* Cattle in herd had not reacted to mammalian tuberculin until the employment of workers affected with pulmonary tuberculosis.

† Positive tuberculin reactors had occurred in herd, although previously there had been no evidence of infection.

‡ Tubercle bacilli of the human type were isolated from the sputum of the patient to whom this animal was exposed.

SUMMARY

Tubercle bacilli with the cultural and pathogenic characteristics of the human type were obtained from lesions of the lung and bronchial

lymph nodes of an adult bovine animal. A lesion was also found in one of the mesenteric lymph nodes. The source of the infection was not determined. The morbid changes are described and the question of the natural infection of cattle with human tubercle bacilli is briefly reviewed.

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LABORATORY AND CLINICAL NOTES

CODLIVER OIL AND TOMATO JUICE IN THE PROPHYLAXIS OF INTESTINAL TUBERCULOSIS[1]

MACK McCONKEY

In a previous communication (1929) attention was directed to the value of codliver oil and tomato juice in the treatment of intestinal tuberculosis; the symptoms were alleviated and the roentgenological evidence of intestinal ulceration disappeared in most instances following the administration of the remedy (1). These observations suggested that the remedy might be used with advantage as a prophylactic measure in intestinal tuberculosis. This view is supported by the experimental work of McConkey and Smith (2) who found that the majority of guinea pigs fed tuberculous sputum developed intestinal tuberculosis when given a diet deficient in vitamin C, but when this diet was supplemented by tomato juice, only a few of the animals showed evidence of intestinal tuberculosis at necropsy.

The present study reveals that the use of codliver oil and tomato juice as a prophylactic measure markedly decreased the incidence of intestinal tuberculosis among our patients. During the years 1926 and 1927, there were 437 patients admitted to Ray Brook, 348 in the moderately advanced and 89 in the advanced stages of pulmonary tuberculosis who were free from symptoms of intestinal tuberculosis at the time of admission; the period of residence ranged from six to nineteen months. The patients in this group did not receive codliver oil and tomato juice as a prophylactic measure and 47, or 10.7 per cent, developed intestinal tuberculosis associated with outspoken symptoms while under our observation. In each of the 47 instances the diagnosis was confirmed by X-ray examination as outlined by Brown and Sampson (3).

In the years 1928 and 1929 codliver oil and tomato juice were first used as a prophylactic measure at Ray Brook. Among the patients admitted during these two years, there was a comparable group of 399 patients, 323 in the moderately advanced and 76 in the advanced stages of the disease. The period of residence ranged from four to twenty-two months. The 399 patients in this group received codliver oil and tomato juice, and only 3, or approximately 1 per cent, developed intestinal tuberculosis associated with outspoken symptoms while under our observation.

[1] From the New York State Hospital for Incipient Pulmonary Tuberculosis, Ray Brook, New York.

This striking decline in the incidence of intestinal tuberculosis may be attributed to the administration of codliver oil and tomato juice since the patients in both groups were under the same sanatorium regimen, the extent of the pulmonary disease was comparable, the duration of residence was approximately the same and there was no material difference in the number receiving collapse therapy, 6 per cent in the first group and 9 per cent in the second. Moreover, for the years 1930 to 1938 inclusive, there were at Ray Brook 913 additional patients in the moderately and far advanced stages of the disease who received codliver oil and tomato juice as a prophylactic measure, and the incidence of intestinal tuberculosis associated with symptoms has remained at the low level of 1 per cent.

There is also an interesting correlation between the decline generally noted in recent years in the clinical incidence of intestinal tuberculosis and the consumption of codliver oil and tomato juice. In 1919 at the Trudeau Sanatorium, Brown and Sampson (3) in a series of 141 patients, 111 in the moderately advanced and 30 in the advanced stages of pulmonary tuberculosis, found X-ray evidence of intestinal tuberculosis in 40, or 28 per cent, at the time of admission. By 1938, the incidence had fallen to approximately 5 per cent.[2] In a similar study at Ray Brook in 1928, comprising 196 patients with comparable pulmonary disease, the incidence was 16 per cent at the time of admission; by 1938 it had fallen to 3 per cent. During the years that this striking decline occurred, there was a marked increase in the use of codliver oil and tomato juice. For the years 1929 to 1938 inclusive, there was approximately a 77-fold increase in the sale of tomato juice. The figures for codliver oil do not include its derivatives and therefore are not so striking (table 1).[3]

Burke and Aronovitch[4] in a series of 109 autopsies on tuberculous subjects in 1938–1939 at the Grace Dart Hospital in Montreal discovered ulcerative intestinal tuberculosis in 76, or 70 per cent. These investigators report that the diet of the patients was deficient in codliver oil and tomato juice or their equivalents.

Dr. Oscar Auerbach writes as follows concerning the incidence of intestinal tuberculosis and the use of codliver oil at Sea View Hospital:

"During the year 1938, there were 143 cases of straight chronic pulmonary tuberculosis which we autopsied. Of these 34, or 22.8 per cent, had no intestinal tuberculosis, while 109 (77.2 per cent) had intestinal tuberculosis. A number of the patients received codliver oil, but there was no regularity in this treatment."

[2] Personal communication.

[3] The data was kindly furnished us by the United States Department of Agriculture, Bureau of Agricultural Economics. No figures were available for the sale of codliver oil and tomato juice prior to 1929.

[4] Personal communication.

It is of interest that the findings of the above contemporary observers approximate those of Louis (4) who in 1846 made the first statistical study of intestinal tuberculosis. In a series of 108 autopsies on phthisical subjects he found tuberculous enteritis in 88, or 81 per cent.

Gardner and Vorwald[5] found that the incidence of ulcerative intestinal tuberculosis in 80 consecutive autopsies on tuberculous subjects who died in Saranac Lake between 1930 and 1934 inclusive was 61 per cent, and that the incidence of intestinal disease in the same number of consecutive autopsies on a similar group of patients who died between 1935 and 1939 inclusive was 41 per cent. Codliver oil and tomato juice, or similar vitamin-containing substances, were given to a much larger percentage of patients in the Saranac

TABLE 1

The sale of tomato juice, citrus fruit juices and codliver oil in the United States during the years 1929–1939 inclusive

YEAR	TOMATO JUICE, #2 CANS	GRAPEFRUIT JUICE, #2 CANS	ORANGE JUICE, #2 CANS	CODLIVER OIL
				gallons
1929–30	220,000	174,000	38,000	2,860,278
1930–31	1607,000	412,000	99,000	2,894,967
1931–32	5550,000	248,000	36,000	1,737,207
1932–33	5536,000	729,000	104,000	1,247,998
1933–34	5072,000	636,000	343,000	3,432,569
1934–35	6688,000	2688,000	1058,000	3,470,259
1935–36	11256,000	2354,000	1177,000	4,607,093
1936–37	16017,000	6267,000	1798,000	5,789,574
1937–38	16941,000	8818,000	1730,000	5,915,964
1938–39	—	—	—	5,218,637

The figures were kindly furnished us by the United States Bureau of Agricultural Economics.

Lake area in the period between 1935 and 1939 than in the period between 1930 and 1934.

Twenty-nine, or 88 per cent, of 33 patients who died of pulmonary tuberculosis at Ray Brook before codliver oil and tomato juice were used as a prophylactic measure presented ulcerative lesions of the gut at autopsy. Of 20 who received this treatment and came to necropsy, only 6, or 30 per cent, had ulcerative lesions of the intestinal tract.

It seems reasonable, therefore, to attribute the decline in the incidence of ulcerative intestinal tuberculosis, in part at least, to increased consumption of fish-liver oils and tomato or citrus fruit juice.

Method of Administration: The method of administration is simple and few patients object seriously to the remedy when it is properly given, but attention

[5] Personal communication.

to detail is important. Three ounces of tomato or citrus fruit juice are placed in a glass about half the size of an ordinary tumbler. On the surface is floated one half ounce (a large tablespoonful) of plain codliver oil. The whole is served ice cold immediately after meals. The patient should be told that slight gaseous eructations savoring of codliver oil may be experienced for the first week or so of treatment, but that they will not be noticeable thereafter. In certain instances we have found it necessary to substitute codliver oil in ten minim capsules for the usual half ounce of oil for a week or so.

CONCLUSION

The present study warrants the conclusion that the administration of codliver oil and tomato juice is a valuable prophylactic measure in intestinal tuberculosis complicating pulmonary tuberculosis.

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LEIOMYOMA OF THE LUNG[1]

Early Course of Tuberculosis

LEOPOLD BRAHDY

CASE REPORT

In September, 1936, an eighteen year old student nurse had a negative chest roentgenogram and negative Mantoux test (to 0.1 and to 1.0 mg. of OT). Six months later her roentgenogram was still negative, but the Mantoux test was positive to 0.1 mg. OT. The roentgenogram in April, 1937 showed a round density at the right base (figure 1). Fluoroscopy showed it was behind the dome of the diaphragm, moved up and down synchronously with it and was inside of the lung. She was admitted to the service of Dr. J. Burns Amberson, Jr., at Bellevue Hospital in October. Detailed studies, including roentgenograms of the gastrointestinal, genitourinary and osseous system, sputum and blood tests, were all negative. The diagnosis of tuberculoma was made and she was transferred to Trudeau Sanatorium in June, 1938.

Sputum examination was positive three times in the first two weeks of her observation there and thereafter was again negative. On December 1, 1938, a typical tuberculous infiltration appeared in the right infraclavicular area (figure 3). The round lesion near the base grew steadily from 1.6 cm. in diameter in April, 1937 to 3.5 cm. in March, 1940 (figures 1 to 4). It seemed desirable to excise this mass.

Accordingly, on March 21, 1940, Dr. W. W. Woodruff operated. On exposure, the lower lobe of the right lung showed a fissure transecting it at the junction of the upper and middle thirds. This made possible resection of the lower two-thirds of the lobe. The patient made an uneventful recovery. The following is the report of Dr. Arthur J. Vorwald, pathologist of the Saranac Laboratory for the Study of Tuberculosis: "The lobe removed at operation showed a localized, round tumor. It measured 2.5 cm. in diameter, was firm and white in color. Section revealed it to be a fibro-leiomyoma. It is interpreted as a benign lesion, unrelated to a tuberculous process. Section of the lobe, somewhat removed from the tumor, revealed an occasional small tubercle."

[1] From the Division of Occupational Diseases and Injuries of Municipal Employees, Office of the Corporation Counsel, City of New York.

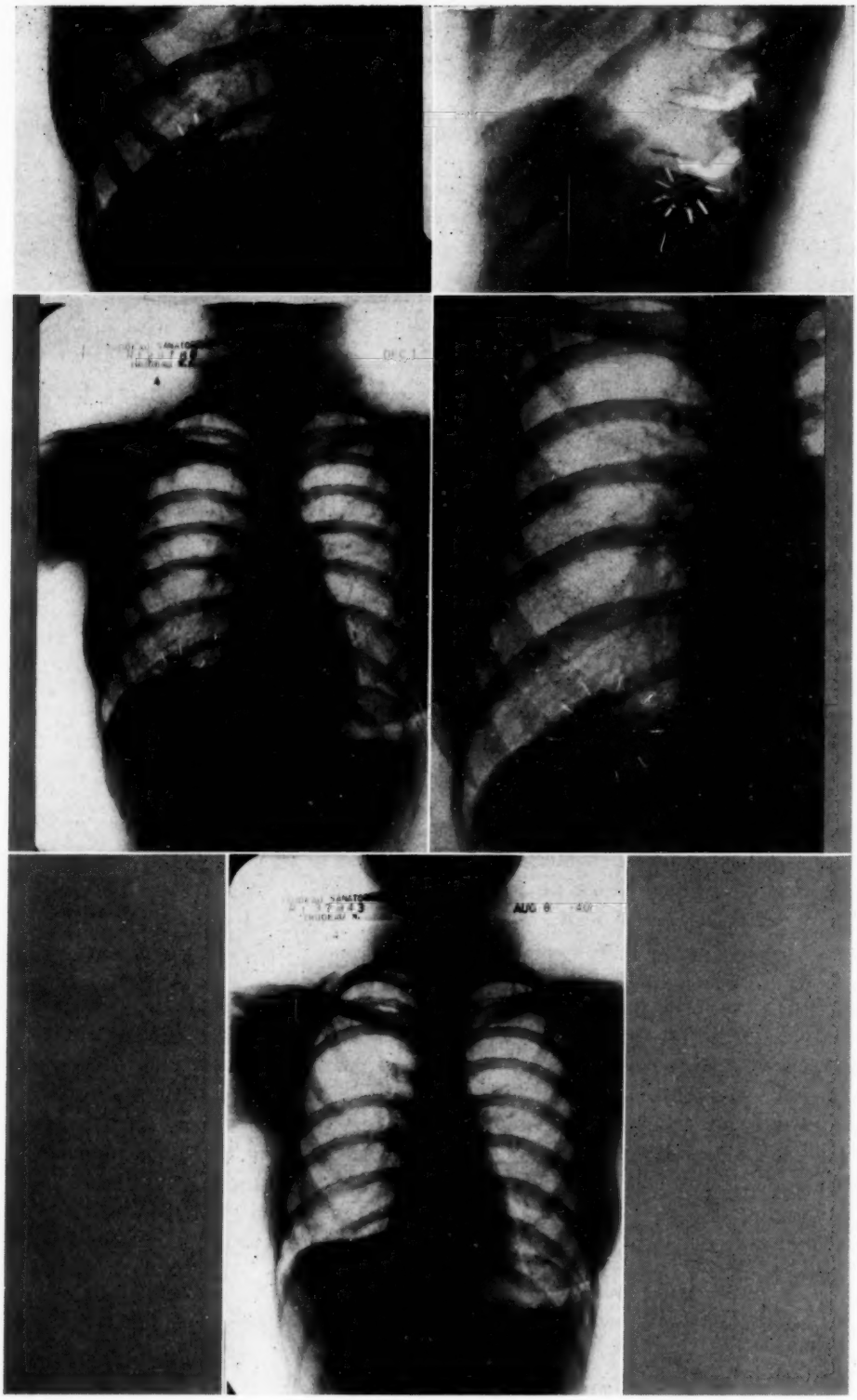

FIG. 1 (top left). April, 1937.
FIG. 2 (top right). June, 1937.
FIG. 3 (left center). December, 1938.
FIG. 4 (right center). March, 1940.
FIG. 5 (bottom). August, 1940.

Two cases of leiomyoma of the lung, both found postmortem, have been reported, as follows:

Deussing, R.: Multiple Primary Myomas of the Lung,—Thesis, University of Munich, 1912.

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Note: Roentgenograms of this tumor were presented at the Röentgen Conference of the American Trudeau Society, Cleveland, Ohio, June 1940, by Dr. Fred H. Heise.

EARLY COURSE OF TUBERCULOSIS

Because a routine roentgenogram revealed a mass suspected of being tuberculoma, the young woman had detailed observation for tuberculosis for twenty months prior to the first roentgenographic evidence of tuberculosis. Observation prior to the first manifestation of disease is necessarily rare. Such a case may throw light on the pathogenesis of the disease. It is, therefore, presented in detail. Except that it caused the whole investigation, the leiomyoma is irrelevant to the development of tuberculosis. In order to keep the subject clear it will not be mentioned. The reader will understand that "normal" roentgenogram means normal *except* for the leiomyoma shadow.

At the age of eighteen the patient was in good health. Past history and physical examination were negative. There was no history of exposure to tuberculosis. In September, 1936, Mantoux tests with 0.1 and 1.0 mg. of OT were both negative. Lung roentgenograms were normal.

During the next few months she was exposed to tuberculosis, and in February the Mantoux test was repeated with 0.1 mg. of OT and gave a positive reaction. The time of the primary infection can, therefore, be fixed between September, 1936 and February, 1937. For convenience in presentation we shall fix the time of the first infection as of December 1, 1936, though it may be shortly before or after.

She was observed a total of four years and at no time had any symptoms of any kind, except slight cough which existed before the original negative Mantoux test of September, 1936. Examinations shown in table 1 were made in the course of the four years.

The important findings are positive sputum examinations in June and July, 1938, eighteen months after the primary infection and five months *before* the first roentgenological evidence of tuberculosis. Her sputum was negative three months before and fourteen months following the first roentgenological sign. No conclusions can be drawn from a single case, but from an epidemicological view, it suggests the question: Is a positive sputum a common occurrence in persons without any roentgenographic evidence of tuberculosis or any symptoms? Is it often the first sign of pulmonary tuberculosis?

The pathological finding in March, 1940 shows two small tubercles in the

TABLE 1

DATE	MONTHS AFTER FIRST INFECTION	ROENTGEN EVIDENCE OF TUBERCULOSIS	MANTOUX	SPUTUM			GASTRIC	SEDIMENTATION RATE (CUTLER)
				Smear	Gaffky	Culture or guinea pig		
								mm.
September, 1936	Prior to infection	Negative	0.1 OT: − 1.0 OT: −					
February, 1937	2	Negative	0.1 OT: +					
October, 1937	10	Negative	0.1 OT: +					
April, 1938	16	Negative						
May, 1938	17	Negative		− −			5/25 smear − G.P. −	12
June, 1938	18	Negative				1 culture − 1 culture +		
June, 1938	18½	Negative	0.1 OT: +	+ +	II III			1.0
July, 1938	19–20	Negative		−				
August, 1938				+ − − −		G.P. + 1 culture − 1 culture +	Smear − Culture − Smear − Culture −	9.5
September, 1938	21	Negative		−				9.5
October, 1938	22–23	Negative		−				
November, 1938				−				6.
December, 1938	24 mos.	Right infraclavicular infiltration (figure 3)		−				7.5

January, 1939 to January, 1940	25 to 37	Series of 10 stereoscopic films. No new lesions. Infraclavicular lesion slowly fading		17 smears −		4 cultures −		At 6 weeks' intervals from 4.5 to 8
February, 1940	39					2 cultures − 1 culture + Confirmed by inoculation of G.P. +	3 cultures − 3 tonsil smears −	
March, 1940	39	Slight decrease (figure 4)						
April, 1940	40			Acid-fast bacilli, not typical of tubercle bacilli	II	1″ spec. Culture − G.P. −		
						2″ spec. Culture − G.P. −		
				−		3″ spec. Culture + G.P. +		
				+				
May, 1940	41			+	II			
June, 1940	42			+	II			
July, 1940	43			−				
August, 1940	44	Lesion fading (figure 5)		−		Culture −		

On these two charts negative is signified by − and positive, by +.

lower lobe which had never been visualized in X-ray films. Dr. Homer L. Sampson reviewed all the stereoscopic roentgenograms in the light of this pathological report. He found no evidence of these tubercles in any of the roentgenograms. It is clear that this patient had a haematogenous spread in spite of the absence of all symptoms and the excellent progress towards healing of the only demonstrable lesion. How old these tubercles were it is impossible to determine but the case raises the question of whether the infraclavicular lesion (the first demonstrable lesion) was of haematogenous origin and the primary infection (implantation lesion) completely invisible by X-ray, as were the tubercles in the lower lobe. On the other hand, as the sputum was positive six months prior to the appearance of the lesion, the question is raised whether bronchogenic spread takes place months before a lesion can be diagnosed. Was the first demonstrable lesion a bronchogenic spread?

SUMMARY

A case is presented with positive sputum six months prior to the X-ray demonstration of tuberculosis with frequent periodic roentgenograms during these six months. For more than a year after the appearance of the tuberculous lesion, the sputum was negative. The sputum then became positive when the lesion was steadily diminishing.

TUBERCLE BACILLI IN AIR AND DUST[1, 2]

EMIL BOGEN AND WILLIAM DUNN

Bacilli in enormous numbers are expectorated by patients suffering from advanced tuberculosis. Careful counts of the number of tubercle bacilli expectorated indicate that the average patient discharges millions of tubercle bacilli daily, though individuals may vary from occasional single to many billions of germs per day (1). With such tremendous production it is not surprising that living tubercle bacilli have been found in the air and dust.

As late as 1937, smears, cultures and guinea pig inoculations were reported to show tubercle bacilli in 55 samples of dust collected from 15 rooms in 5 different tuberculosis institutions in Pennsylvania and New Jersey, while specimens from a dormitory in a fire station and several business offices taken as controls remained uniformly negative (2).

There is a great difference between the spread of tubercle bacilli by careful patients who conscientiously dispose of their sputum, and careless ones who expectorate freely throughout the room (3). It has been suggested that guinea pigs might be made useful pets of patients with tuberculosis, similar to canaries or white mice kept by miners, as infection of these animals would be striking evidence that precautions have been neglected and the danger of infection to others exists.

That the dust and air at the Olive View Sanatorium does not contain viable tubercle bacilli to any appreciable extent, is indicated by the fact that more than 15,000 guinea pigs have been bred at this institution during the past two decades without ever developing tuberculous infection. Before use in any experiment here, each animal has been skin-tested with 5 mg. of Old Tuberculin, with uniformly negative results, though infection in these animals is consistently followed by strongly positive tuberculin tests. Moreover, a number of children of employees, living on the grounds of this sanatorium for many years, remain persistently tuberculin-negative.

In view of the positive findings reported, even in sanatoria described as modern and well conducted, however, a repetition of this study was attempted here. Petri dishes, containing 20 cc. of normal salt solution, left uncovered became completely dry within a few days. In view of this rapid evaporation

[1] From the Olive View Sanatorium, Olive View, California.

[2] With the aid of Works Progress Administration, Project No. 665-07-3-223, Los Angeles County, California.

here, which might have resulted in death of organisms through desiccation, 5 per cent glycerine was added to the salt solution in order to keep the contents of the dish moist. Such plates were then exposed in various locations throughout the institution, on eight different occasions, for periods of one week each. The contents of the plates were then carefully washed out with distilled water into test tubes, shaken with equal volumes of 4 per cent sodium hydroxide for half an hour, centrifuged, the sediment examined microscopically and inoculated into cultures and guinea pigs.

In addition, control plates were placed in a sheltered spot for a week, after the addition of a known amount of a living stock culture of tubercle bacilli, and then similarly treated and examined. Such controls have been uniformly positive, and indicate that if living organisms had fallen on these dishes they would probably have been detected through these measures, though there is some decline in the number of organisms remaining viable after a week's exposure. Contamination of Corper's, Petragnani's and Jensen's culture media here used was rendered infrequent by the treatment with alkali.

Altogether, 94 Petri dishes were exposed in various parts of the institution and then examined for tubercle bacilli. Five specimens revealed a few isolated organisms by culture; in two, rare bacilli were seen on smear, and one was confirmed by a positive guinea pig finding. The source of the positive material in every case was one where the danger of contamination was obviously greatest, being on one of the admitting wards where patients who had not yet received adequate instructions may enter, or in a location in the laboratory where large amounts of heavily infected sputum are handled. Two of the positive cultures were obtained from among 18 plates exposed in the admitting wards, and the three other positives were found among 35 plates exposed in various sites in the laboratories. Not a single positive culture was obtained on plates from the wards containing patients who had already received their instructions in the admitting room, or in other parts of the institution outside of the admitting wards and the sputum examining room in the laboratory.

CONCLUSION

Microscopical examinations, cultures and guinea pig inoculations of dust collected in various parts of the Olive View Sanatorium indicate that visible or viable tubercle bacilli are not to be expected in most parts of the institution, and that even in the admitting wards and the laboratories such contamination is relatively rare. These findings agree with previous clinical observations that, in this institution, the danger of dust-borne or air-borne tuberculosis infection is negligible. Studies in other institutions using adequate technique in the care of tuberculosis patients similarly show an absence of organisms, which may be abundant and ubiquitous if these precautions are neglected (4). On the other hand, it is recognized that, even under the best conditions, the

opportunities for infection increase with intimacy of contact, and that workers caring for patients with tuberculosis can only be shielded from exposure to such infection by conscious and conscientious precautions. The danger of direct and droplet transmission of infection remains high in the immediate vicinity of patients with open tuberculosis. By relatively simple measures, however, the air and dust in the general vicinity may be kept free from these dangerous germs.

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GASTRIC CONTENTS IN TUBERCULOUS CHILDREN[1]

CLEAVELAND FLOYD AND ELI FRIEDMAN

The importance of the examination of the fasting gastric contents of tuberculous patients for tubercle bacilli was first called to the attention of the medical profession by Meunnier (1) and has now been universally adopted as a valuable aid in the diagnosis of pulmonary tuberculosis, particularly in adults who have little or no sputum and in infants and young children who, instead of expectorating, cough up mucus and then swallow it. In fact, this method of searching for tubercle bacilli in the sediment of gastric contents of adults not raising sputum and in children has become a routine procedure in many sanatoria, and in the recent edition of Diagnostic Standards of the National Tuberculosis Association it is suggested that a patient with no sputum should not be classified as apparently cured until the gastric contents have been thoroughly examined for tubercle bacilli and found negative.

It has been found that every case showing tubercle bacilli in the gastric contents gave a positive tuberculin test, indicating the presence of a tuberculous focus somewhere in the body sufficient to elicit the allergic response. The only problem is to locate the site of the focus. If we rule out primary tuberculosis of the stomach because of its rarity and primary tuberculosis of the tonsils and adenoids because of lack of evidence of cervical adenitis, we must agree with Armand-Delille that the source of tubercle bacilli in the gastric contents, in the vast majority of cases, must be an unhealed pulmonary lesion or a caseous tuberculous lymph node which has ulcerated into a bronchus. Tubercle bacilli are coughed up and swallowed, resulting in the contamination of the gastric contents.

Since the presence of tubercle bacilli in the gastric contents is obviously an indication that we are dealing with a case of tuberculosis in which the tuberculous focus is not completely healed, the frequency with which positive findings are obtained will depend entirely on the type of case examined. When the patient presents an active parenchymatous involvement of the lung, there is a much greater probability of finding viable tubercle bacilli than when we are dealing with a case who has a healed Ghon's tubercle or healed lymph node.

The use of Meunnier's method has been largely confined to the cases of actual and suspected tuberculosis in infants and young children. Investiga-

[1] From the Boston Tuberculosis Association, Boston, Massachusetts.

tion of the older children and young adult group has been limited. Yearly, many hundreds of children who have been in close contact with tuberculosis are gathered in preventoria or summer camps. Beyond the fact that the tuberculin test is positive and physical and chest X-ray examinations show no parenchymatous pulmonary lesion, little is known about them. The home contact is temporarily broken but this, in certain instances, may be to a degree replaced by the child carrying the tubercle bacillus in the gastric contents. To secure some data on this problem the following study was undertaken.

Methods of procedure: Gastric lavage was carried out on 105 children between the ages of six and twelve years. All of these children came from tuberculous families and all reacted to tuberculin. A small number showed roentgenological evidence of a calcified Ghon's focus and a few presented some calcification of a hilar lymph node but without any reaction at the hilum. In every child the fasting stomach was washed with 200 cc. of sterile saline. The washings were then centrifuged and 2 cc. of the sediment were injected into the peritoneal cavity of a guinea pig. Smears of the sediment were also stained for tubercle bacilli. In 50 children lavage was repeated on two successive occasions and the contents obtained were combined and used for inoculation. This procedure was adopted to increase, if possible, the number of positive results as advocated by Paulsen and Andersen. After a six weeks' period of observation, the animals were autopsied and examined for tuberculosis. Twenty-one of the guinea pigs died of infection within three weeks and were discarded. The remainder, 83, were available for study.

Of the 83 inoculated pigs, 3 showed lesions from which the tubercle bacillus was recovered. Three others had lesions of lymph nodes or spleen but no organism could be obtained. The percentage of positive results was 3.6, and this, in all probability, would have been much higher except for the loss of so many animals from intercurrent infection.

X-ray findings in the 3 positive cases all showed involvement of the hilar lymph nodes. In cases in which the results were in doubt the chest films were repeatedly negative in 2, and in the third the hilum shadows were only slightly increased. In 5 of the animals showing positive or questionable lesions, the retroperitoneal or mesenteric nodes were involved. It is unfortunate that the material obtained from the 3 doubtfully positive animals was not reinjected. One of the positive cases, in addition to a calcified node in the left hilum, had a tuberculous area in the muscle sheath near the left hip, removed surgically two and one-half years previously. It may have been a secondary focus to an initial infection in the hilar nodes. In the last few weeks, while under study, a Ghon's tubercle appeared in the lower left lung field. Apparently, a healed secondary focus does not rule out the possible persistence of open primary focus, and this association of positive gastric contents and surgical tuberculosis suggests the desirability of the use of the

method of Meunnier in extrapulmonary tuberculous lesions in order to determine whether endogenous infection is likely to be recurrent.

CONCLUSIONS

In a study of the fasting gastric contents of 83 children from families having tuberculosis, 3.6 per cent were found to be positive; an equal number showed questionable lesions in the inoculated animals. These results demonstrate the desirability of the use of this method in the age group between six and twelve years where there is no definite evidence of open tuberculosis to determine its presence. Its value in the field of preventive medicine is self-evident and its wider use may throw further light on the question of endogenous tuberculous infections.

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ISOLATION OF TUBERCLE BACILLI[1, 2]

A Comparison of Various Media for Primary Isolation of the Tubercle Bacillus from Pathological Material

ELEANOR ALEXANDER-JACKSON

One of the chief problems in the examination of specimens from suspected cases of tuberculosis is that of improving cultural methods for the detection of tubercle bacilli in pathological material that contains few or no demonstrable acid-fast bacilli. Development of culture media optimal for growth of tubercle bacilli, as well as the improvement of methods of concentration of the specimen, has engaged the constant attention of workers in this field. While many have compared the cultural method with guinea pig inoculation, few seem to have studied the relative efficiency of different media inoculated with specimens from lesions rather than with dilute suspensions of pure cultures. It is well known that tubercle bacilli present in small numbers are more difficult to cultivate directly from sputum, tissue or body fluids than from laboratory cultures.

This study of 45 specimens was undertaken to compare the ability of four well known media and modifications of them to support growth from material containing few tubercle bacilli. It was also considered of interest to determine, if possible, whether any one of these media appeared sufficiently superior to warrant its recommendation as the sole medium for diagnostic culture work.

In 1934 the writer (1) reported that true S-colonies of the human tubercle bacillus could be obtained and maintained on Bordet-Gengou medium that contained an optimal trace of ferric chloride, 0.000,4 per cent. Subsequently, it was observed that this modified Bordet-Gengou medium often supported more luxuriant growth than the original, when very dilute suspensions of tubercle bacilli were employed as inoculum, and, also, that colonies tended to appear a few days earlier. These observations had been made on two human strains, No. 3828 and "Arilotta," which at that time had recently been isolated. Mishulow (2) had previously reported the original Bordet-Gengou and Löwenstein media equally effective for the isolation of human tubercle bacilli, but the Bordet medium superior for isolating the bovine type.

[1] From the Division of Laboratories and Research, New York State Department of Health, Branch Laboratory, New York City.

[2] This work was made possible by a grant from the Rosenwald Family Fund.

It seemed worth while, therefore, to compare both modified and unmodified Bordet-Gengou media with several of the egg media now in use, namely, Löwenstein's, Petragnani's, and Corper's egg yolk (3), for the primary isolation of tubercle bacilli from pathological material, such as sputum, urine, pus and pleural fluids. Almost all of the specimens were obtained from tuberculous patients, some from cases diagnosed as "suspicious." Five control fluids were from patients with a diagnosis of carcinoma (four of the lungs, one of the liver). Six specimens were sputa, 2 urine, one pus, one knee joint fluid, one gastric lavage, one asicitic fluid and the remainder chest fluids.

Substances other than ferric chloride were added to the media used at various times, in order to determine whether any of them might prove more stimulating to growth. The interesting studies of Mueller (4, 5) and of Williams (6) and other workers on growth accessory substances and food requirements of bacteria suggested that although potato and blood in Bordet medium already contain minute traces of one or more of such substances, additional amounts of some of the chemicals they had used for the diphtheria bacillus and other microörganisms might also promote growth of the tubercle bacillus. Small amounts of the following substances were added, respectively, to Bordet-Gengou medium just prior to adding the blood: pimelic acid, nicotinic acid, mixtures of these two with and without ferric chloride, pantothenic acid, and two plant hormones, indol-acetic and indol-butyric acid.

Petragnani's medium, Bordet-Gengou medium and ferric chloride Bordet-Gengou medium were employed in every attempt. Holmes' modification (7) of Löwenstein's medium and Corper's egg-yolk medium were employed on four occasions, as was the original Löwenstein medium with the Holmes modification. In practically all of the specimens, few or no acid-fast bacilli were seen on film preparations of the sedimented material; this was thought to constitute a more rigid test of the media than if the material contained a considerable number of the bacilli.

TECHNIQUE

Sputa were treated by the Hanks (8) method of digestion and concentration. This resembles the Petroff sodium hydroxide method, but the Hanks hydroxide digestor contains 0.2 per cent of potassium alum and 0.002 per cent of bromthymol blue indicator. Hanks and his collaborators claim that the sediments obtained after neutralization with 2.5 N hydrochloric acid and centrifugation, contain considerably larger numbers of acid-fast rods than if sodium hydroxide alone is used. A film preparation stained by the Ziehl-Neelsen method was made of each sediment.

Body fluids were first tested for bacterial growth on a blood-agar plate, then centrifuged and films stained by the Ziehl-Neelsen method made of the sediments.

Two drops of sediment slightly diluted with sterile distilled water were seeded on each slant with a 1 ml. pipette in a manner to permit a spread over the entire surface of the slant. At least 3 and sometimes 6 fresh slants of each medium were employed for each specimen. They were incubated at 37°C. for at least six weeks and were examined every few days. Only growth, no growth and contaminations are indicated in the table.

RESULTS

The results of the microscopical and cultural study of the 45 specimens are presented in the table. Definite growth of the tubercle bacillus was obtained from 23 of the specimens.

From the table it will be seen that there were 5 instances in which growth appeared on the original or modified Bordet-Gengou medium but failed to appear on the egg media, and one instance in which growth occurred on Löwenstein's and Petragnani's media and failed to appear on the Bordet-Gengou media. Petragnani's proved the best of the egg media, but Löwenstein's was almost as satisfactory. This is in general agreement with results obtained by Whitehead (9) in comparing Petragnani's, Löwenstein's, Corper's potato and Petroff's media. It was found that Löwenstein's medium containing malachite-green was more resistant to contaminants other than molds than that containing Congo-red.

The results obtained with the Bordet-Gengou medium modified by the addition of traces of ferric chloride, pimelic, nicotinic and pantothenic acids were, on the whole, slightly superior to those obtained with unmodified Bordet-Gengou and the egg media, in that growth sometimes appeared several days earlier and was often more luxuriant. None of the above mentioned growth-promoting chemicals seemed to be any more stimulating than the trace of ferric chloride.

Löwenstein's original formula which contains potassium acid phosphate, KH_2PO_4 gave more luxuriant growth than Holmes' modification which substitutes potassium sulphate, K_2SO_4. However, 2 of 9 specimens yielded a little growth on one of 3 tubes of Holmes' medium, while none appeared on the 3 tubes of the original Löwenstein medium.

With 4 specimens in which more than an occasional acid-fast rod was seen in stained film preparations of the sediment, growth of the bacilli occurred about equally well on all the media, with the exception of the Bordet-Gengou, plus plant hormones, indol-acetic and indol-butyric acid, all of which appeared to inhibit growth.

Better growth was obtained with the Bordet-Gengou medium tubed at about 52°C. than at 45°C. (10). At the higher temperature, the slants should be dark red rather than bright cherry red. In preparing Bordet-Gengou medium (11, 12, 13) with ferric chloride, a 10 per cent stock solution of ferric

TABLE 1

Comparison of various culture media in the primary isolation of tubercle bacilli from 23 of 45 pathological specimens

TYPE OF SPECIMEN	STAINED FILM PREPARATION OF SEDIMENT*	MEDIA							MEDIA ON WHICH GROWTH WAS FIRST NOTED	NUMBER OF DAYS AFTER INOCULATION WHEN GROWTH FIRST NOTED
		Bordet-Gengou unmodified	Bordet-Gengou + $FeCl_3$ 0.000,4%	Bordet-Gengou + other growth promoting substances†	Petragnani	Löwenstein (Holmes modification)	Löwenstein (original)	Corper's egg yolk		
Chest fluids	−	No growth	Growth		No growth				B-G + $FeCl_3$	27
	−	No growth	Growth		No growth				B-G + $FeCl_3$	27
	+	Growth	Growth	Growth	Growth	Growth		Growth	B-G + $FeCl_3$, Petragnani's	11
	+	Growth	Growth	Growth	Growth	Growth		Contaminated	B-G, B-G + $FeCl_3$	19
	++	Growth	Growth	Growth	Growth	Growth		Growth	All media	17
	+	Growth	Growth	Growth	Growth	Growth		Growth	All media	17
	−	Growth	Growth	Growth	Growth	No growth		Growth	B-G and B-G + $FeCl_3$	17
	−	Growth	Growth		No growth	No growth	No growth	No growth	B-G, B-G + $FeCl_3$	48
	+	Growth	Growth		No growth	No growth	No growth	No growth	B-G, B-G + $FeCl_3$	48
	+	No growth	No growth		Growth	Growth	No growth	Growth	Löwenstein's, Petragnani	48
	++	Growth	Growth		Growth	Growth	Growth	No growth, medium dry	All media	25
	−	No growth	Growth scant	Growth	No growth			No growth	B-G + $FeCl_3$	12
	−	Growth	Growth	Growth	No growth			No growth	B-G, B-G + $FeCl_3$	7
	−	Growth 1 colony	No growth		No growth	Growth	No growth		B-G	27
	1 bacillus ±	Growth	No growth		Growth	Growth	Growth		Petragnani's, Löwenstein (original)	17

Sputa	−	Growth	Growth		Growth	Growth	Growth	Growth	B-G + $FeCl_3$ and Löwenstein's	16
	−	Growth	Growth	Growth	No growth			No growth	B-G + $FeCl_3$	7
	++	Contaminated	Contaminated		Growth	Growth	Growth		Petragnani's	17
	++	Growth	Growth		Growth	Growth	Growth		All media	17
Urines	+	No growth	Growth	Growth	Growth			No growth	B-G + $FeCl_3$, Petragnani's	12
	+	Growth	Growth	Growth	Growth			No growth	B-G, B-G + $FeCl_3$	7
Pus	−	Growth	Growth	Growth	Growth			Growth	B-G + $FeCl_3$	7
Gastric lavage	−	Contaminated	Contaminated		Growth	Contaminated	Contaminated		Petragnani's	22

* − = no acid-fast bacilli, + = occasional acid-fast bacillus, ++ = more than an occasional acid-fast bacillus.

† Growth promoting substances include pimelic, nicotinic and pantothenic acids in several concentrations and combinations.

chloride should be made fresh every few months and kept at refrigerator temperature.

SUMMARY AND CONCLUSIONS

A cultural study of 45 pathological specimens for the isolation of tubercle bacilli was made in which 4 egg media (Petragnani's, Löwenstein's, Holmes' modification of Löwenstein's and Corper's) and the original and modified Bordet-Gengou media were employed. Growth of tubercle bacilli was obtained from 23 of the specimens. Five of these cultures were isolated on the Bordet-Gengou media, but failed to develop on any of the egg media, and one culture grew on the egg media but not on either one of the Bordet-Gengou media.

From these results it appears that while almost all of these media are valuable in the primary isolation of tubercle bacilli from pathological specimens, no single medium is sufficient to ensure isolation from material that contains very few microörganisms. Therefore, when such specimens are to be cultured for the presence of tubercle bacilli, at least two media should be employed,[3] one egg medium, such as Petragnani's or Löwenstein's, and the Bordet-Gengou medium in its original formula or modified by the addition of ferric chloride. If only one medium is used, Petragnani's or Löwenstein's medium with malachite-green dye would be preferable, since they are more resistant to contaminants than the Bordet-Gengou medium.

Almost all of the material used in this study was obtained through the laboratory of Tuberculosis Service at Bellevue Hospital, Dr. J. Burns Amberson, director, and Miss Ruth Egan, bacteriologist. Their kind coöperation is greatly appreciated.

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A PNEUMOTHORAX SOUND FILM

This film was produced by Capitol Films; it was written by Drs. J. S. Edlin, S. Bassin and W. Lichtenberg. It demonstrates the indications and technique of therapeutic pneumothorax including its major complications. The pictures are clear; the text in simple didactic manner is generally well suited for undergraduate and postgraduate teaching. Many roentgenograms are shown in illustration of the spoken word. An interesting feature is a sequence of cinematographic fluoroscopy during intrapleural air injection.

The running time is thirty minutes. The film is available for rental and sale. Further information may be had on request from the National Tuberculosis Association.

TUBERCULOSIS IN THE RAT[1,2]

I. Gross Organ Changes and Tuberculin Sensitivity in Rats Infected with Tubercle Bacilli

C. C. WESSELS

It has been demonstrated experimentally by several workers (1) that the albino rat is resistant to tuberculosis. The absence of typical tubercle formation in its tissues and organs is often stressed. Other workers (2) (3), however, have observed that the rat, although highly resistant to the disease, can be infected with virulent strains of tubercle bacilli and that gross lesions of tuberculosis develop in the lungs within a period of from three to five months.

In the study here reported an endeavor was made to investigate the disease in the rat, in an effort to throw more light on the mechanism of natural resistance to tuberculosis. This was attempted by determining the fate of the tubercle bacillus when introduced into the body of the albino rat and by correlating this fate with the histological changes that took place in the various organs where the bacilli had localized.

EXPERIMENT I: ORGAN CHANGES

Six groups of Wistar albino rats were infected with tubercle bacilli as follows:

Group 1: 12 rats were infected intravenously with 0.1 mg. of *M. tuberculosis*, bovine type (Ravenel strain).
Group 2: 12 rats were infected intravenously with 0.001 mg. of *M. tuberculosis*, bovine type (Ravenel strain).
Group 3: 3 rats were infected intravenously with 0.1 mg. of *M. tuberculosis*, human type (P 15 b strain).
Group 4: 3 rats were infected intravenously with 0.001 mg. of *M. tuberculosis*, human type (P 15 b strain).
Group 5: 3 rats were infected intravenously with 0.1 mg. of *M. tuberculosis*, avian type (Avian 12).

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.
[2] Presented in partial fulfillment for the degree of Doctor of Veterinary Medicine, University of Pennsylvania.

Group 6: 3 rats were infected intravenously with 0.001 mg. of *M. tuberculosis*, avian type (Avian 12).

The bovine strain, Ravenel, was isolated many years ago from a tuberculous cow and is still highly virulent for rabbits and guinea pigs. As few as 30 inhaled bacilli will cause fatal tuberculosis in rabbits within three to six months, and doses of 0.000,1 mg. injected intravenously cause rapidly progressive disease.

The human strain, P 15 B, was isolated in 1923 from the lung of a human being who died from pulmonary tuberculosis. It has the virulence for rabbits and guinea pigs characteristic of the human type.

The avian strain, Avian 12, was isolated from the spleen of a chicken in 1929. In 1936, when the work detailed in this study was conducted, 1.0 mg. of this microörganism injected intravenously killed rabbits with the Yersin type of tuberculosis in three to four weeks. Its virulence, therefore, was typical of the avian type.

Prior to the commencement of this experiment, the rats were subjected to the tuberculin test; all were tuberculin-negative.

Rats from each series were killed twenty-four hours after infection with the different types of tubercle bacilli; none revealed macroscopical changes in any of the organs or tissues. No tubercle bacilli were seen in smears from any of the organs.

Infection with Bovine Type Bacilli: One week after infection with 0.1 mg. of bovine type tubercle bacilli there was marked enlargement of the liver, spleen and tracheobronchial lymph nodes. Smears from the different organs revealed the presence of bacilli, except in the kidneys.

Two weeks after infection the enlargement of the liver, spleen and tracheobronchial lymph nodes was still conspicuous. The lungs were slightly hyperaemic and oedematous. There were numerous more or less circumscribed, grayish-white, pin-point sized nodules of glassy appearance throughout the lungs. Smears showed bacilli in the liver, spleen and lungs. In one case the bone marrow showed the bacilli in nests.

At the end of a month the enlargement of the spleen and tracheobronchial lymph nodes persisted. The liver appeared normal. In the lungs, nodules like those described above persisted. Bacilli were found in the liver, spleen, tracheobronchial lymph nodes and lungs.

Two months after infection, the spleen and the tracheobronchial lymph nodes were greatly enlarged. Again the lungs showed the char-

acteristic nodules, but these were in a more advanced stage. They were more numerous and groups had become confluent, so as to form large irregular masses. The spleen and lungs showed bacilli in large numbers.

After three months the enlargement of the spleen and tracheobronchial lymph nodes was still evident. The lungs were studded with grayish, conglomerate, irregular nodules. Bacilli were found in the lungs, spleen, tracheobronchial lymph nodes and liver.

The macroscopical changes in the various organs at the same intervals after infection with 0.001 mg. bovine type tubercle bacilli were essentially similar to those found after a large dose, except that the involvement was less extensive. Bacilli were found in the lungs only, during the first month of infection. Later bacilli were demonstrated in the liver, spleen and lymph nodes as well.

Infection with Human and Avian Type Bacilli: The effects of human and avian type tubercle bacilli were similar. Two weeks after infection with 0.1 mg. of human tubercle bacilli, there were no changes in the liver and kidneys. There was, however, a tremendous enlargement of the spleen, the surface of which was peppered with miliary, pin-point sized, sharply circumscribed, grayish-white nodules. The lungs also showed a few of the nodules already described. Numerous bacilli were seen in the lungs, but none in the liver, spleen, tracheobronchial lymph nodes or kidneys.

Two months after infection with human type bacilli there was a marked splenic enlargement. The lungs were studded with nodules, which in part had become confluent. The tracheobronchial lymph nodes were increased to several times the normal size. Bacilli were found only in the lungs and only in small numbers.

Essentially the same changes were found in the different organs of rats injected with 0.001 mg. human type tubercle bacilli, but they were less extensive than with the larger dose.

Two weeks after infection with 0.1 mg. of avian type tubercle bacilli, there was a tremendous enlargement of the liver, tracheobronchial lymph nodes and spleen. The lungs were peppered with nodules like those already described. The liver, spleen and lungs contained numerous bacilli, but bacilli were not found in the tracheobronchial lymph nodes or kidneys.

Two weeks after infection with 0.001 mg. of avian type tubercle bacilli, there was a slight enlargement of the liver, spleen and tracheobronchial lymph nodes. Two months after infection with this dose the spleen

was only slightly enlarged, but the hypertrophy of the tracheobronchial lymph nodes was extensive. The lungs showed several very small isolated pin-point sized nodules. No bacilli could be found in the organs.

At no time did any of the infected rats show clinical symptoms of disease, irrespective of the type of organism used. In spite of the infection, even after three months, the rats developed normally and gained in weight. At no stage of the disease were there any signs of caseation in any organ or tissue.

EXPERIMENT II: TUBERCULIN SENSITIVITY

While the nature of caseation is not definitely established, there are many facts, especially the work of Rich and Lewis (4), which suggest that sensitivity to tuberculin protein plays an important rôle in its genesis. Clinical symptoms also are commonly correlated with tuberculin sensitivity. In view of the absence of caseation and symptoms of toxicity an attempt was made to determine if tuberculin sensitivity occurs in rats.

In this experiment, intracutaneous tuberculin injections of Old Tuberculin in 1 to 10 dilution were given to a group of infected rats. In most of the cases a simultaneous injection of control broth was given on the opposite side. Dimensions of the resulting swellings are given in millimetres in table 1.

At autopsy all the rats of the series revealed marked macroscopical changes of the lungs, tracheobronchial lymph nodes and, in some cases, the spleen as well. These have already been described. The lungs, liver, spleen and tracheobronchial lymph nodes of each rat revealed tubercle bacilli on culture. This will be described in a subsequent paper. It is therefore apparent that these rats were infected with the various types of tubercle bacilli.

All the swellings which developed after intracutaneous tuberculin injection in the infected rats were of the same nature, namely oedematous, and, in most cases, diffuse and vaguely defined. In no instance was there any redness or necrosis in these areas.

In view of the fact that most of the rats, prior to infection, were completely negative to tuberculin, and since they never showed any swellings at sites of control broth injections, it is evident that the infected rats did respond with sensitivity to tuberculin.

These reactions are atypical, as they do not correspond to the char-

acteristic tuberculin reaction in several respects. Similar observations have been made by Hehre and Freund (15). The cytological picture of

TABLE 1

RAT NUMBER	INFECTIVE DOSE OF TUBERCLE BACILLI	NUMBER OF DAYS AFTER INFECTION	TUBERCULIN REACTION AND SIZE IN MILLIMETRES	CONTROL BROTH INJECTIONS	MACROSCOPIC TUBERCULOSIS	TUBERCLE BACILLI
11	0.1 mg. bovine	32 48	DOS marked 17 x 13 x 0.4 DOS 9 x 9 x .5	Neg. Neg.	++++	Lung, liver, spleen, node and kidney
5	0.1 mg. bovine	31 58	DOS DOS 30 x 10 x 1.5	Neg. Neg.	++++	Lung, liver, spleen, node and kidney
12	0.1 mg. bovine	30 57 88	DOS marked DOS 11 x 12 x 2 DOS 5 x 5 x 1	Neg. Neg.	++++	Lung, liver, spleen, node and kidney
6	0.1 mg. bovine	31 58 88	DOS DOS marked 37 x 22 x 1.5 DOS 10 x 10 x 1.5	Neg. Neg. Neg.	++++	Lung, liver, spleen, node and kidney
27	0.1 mg. human	35 56	DOS 12 x 14 x .5 Insignificant nodule	Neg. Neg.	++++	Lung, liver, spleen, node and kidney
16	0.001 mg. bovine	26	OS 6 x 5 x 1.5	Neg.	+++	Lung, liver, spleen, node and kidney
22	0.001 mg. bovine	28	OS 9 x 9 x 1.5	Neg.	+++	Lung, liver, spleen, node and kidney
17	0.001 mg. bovine	26 55	OS 5 x 4 x 1 OS marked 28 x 20 x 2.5	Neg. Neg.	+++	Lung, liver, spleen, node and kidney
23	0.001 mg. bovine	28 50	Neg. Neg.	Neg. Neg.	+++	Lung, liver, spleen, node and kidney

TABLE 1—*Concluded*

RAT NUMBER	INFECTIVE DOSE OF TUBERCLE BACILLI	NUMBER OF DAYS AFTER INFECTION	TUBERCULIN REACTION AND SIZE IN MILLIMETRES	CONTROL BROTH INJECTIONS	MACROSCOPIC TUBERCULOSIS	TUBERCLE BACILLI
18	0.001 mg. bovine	26 55 83	OS 5 x 8 x 1 OS marked 28 x 20 x 1.5 OS 9 x 9 x 1	Neg. Neg. Neg.	+++	Lung, liver, spleen, node and kidney
24	0.001 mg. bovine	28 50	OS 6 x 7 x 1 Insignificant nodule	Neg. Neg.	+++	Lung, liver, spleen, node and kidney
30	0.001 mg. human	31 53	Neg. Insignificant nodule	Neg. Neg.	++	Lung, liver, spleen, node and kidney
36	0.001 mg. avian	30 58	Neg. with human O.T. Insignificant nodule with avian O.T.	Neg. Neg.	++	Lung, liver, spleen, node and kidney

D: Diffuse. O: Oedematous. S: Swelling.

the tuberculin reaction in the rat resembles the true tuberculin reaction in that the cellular infiltration (figure 1) is mononuclear; at no stage is there any polymorphonuclear infiltration, nor is there any necrosis (6).

It is noteworthy that Dienes and Mallory (5) have recently pointed out that the inflammation of the tuberculin type of sensitization is associated in its milder form by a predominance of mononuclears. The polymorphonuclear infiltration of more intense tuberculin reactions is associated with necrosis of tissue. Since the rat develops but a mild sensitivity to tuberculin the absence of polymorphonuclears from the reaction is understandable.

From the data on hand, it appears that there is some correlation between the degree of infection and the response of the host to tuberculin. As can be seen in the table, the degree of inflammation was greater in rats infected with large doses, which exhibited more extensive changes in their organs than did rats infected with smaller dosages.

Unfortunately the dimensions of the swellings at the sites of tuberculin injection, one month after injection, were not taken in all instances, which makes it impossible to state whether there is an increase in intensity of the reaction from the first to the second months. However,

it appears that there is a definite decrease in intensity of reaction from the second to the third month. Thus the tuberculin skin hypersensitivity in the rat, slight though it is, reaches a certain height and then declines in the course of the disease.

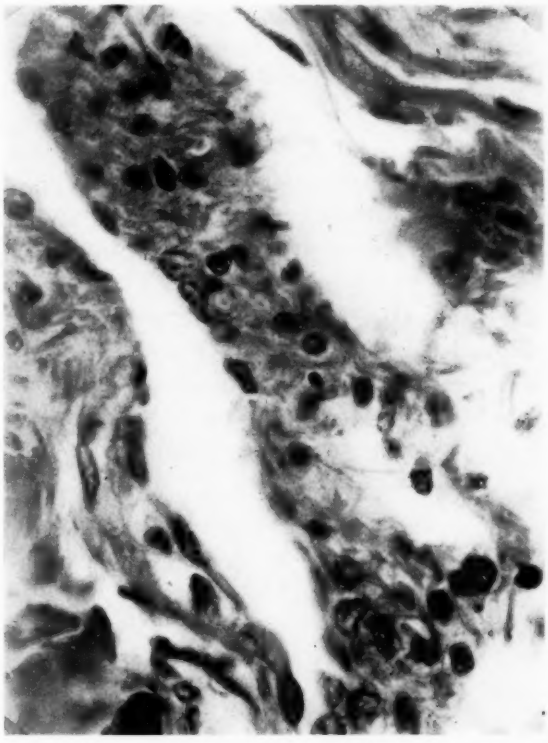

FIG. 1. Tuberculin reaction in a rat infected with tubercle bacilli. There is mononuclear leucocytic infiltration only. Magnification × 1000.

It has been shown by several authors (7, 8) that the general toxic reaction of sensitized animals to tuberculin does not always parallel the skin reaction. Therefore, the following data have been obtained.

Six rats, two to three months after infection with bovine or human type tubercle bacilli, received undiluted tuberculin intraperitoneally. Two of these died during the following night. One had been injected with 1.0 cc., two months after infection with 0.1 mg. bovine type bacilli. At necropsy this rat showed congestion of the internal organs and fluid in the peritoneal cavity. The other received 0.5 cc. of undiluted tuber-

culin two months after infection with 0.1 mg. human type tubercle bacilli. The remaining 4 rats, infected two to three months previously with 0.001 mg. bovine or human type tubercle bacilli, survived an intraperitoneal injection of 0.25 to 1.25 cc. of undiluted tuberculin.

It appears, therefore, that rats with extensive tuberculous changes can be killed by massive doses of tuberculin. However, the general toxicity of tuberculin for the tuberculous rat is only slight, corresponding with the mild and atypical skin sensitivity developed by these animals.

EXPERIMENT III: SENSITIZATION WITH TUBERCULIN PROTEIN

Up to the present all evidence indicates that the active principle of tuberculin is associated with the protein fraction manufactured by the tubercle bacillus. It has also been shown that this protein, in chemical composition and biological potencies, behaves like many other proteins (9). It has been found (10) that repeated injections of this tuberculoprotein in amounts equivalent to other proteins, such as crystalline egg albumen and horse serum similarly injected, sensitize animals to a high degree so that they exhibit the typical Arthus phenomenon. An effort was made to determine if rats can be similarly sensitized to tuberculin protein.

In this experiment the so-called TPT (11), the tuberculin-protein precipitated from unheated tuberculin by trichloracetic acid, was used to sensitize normal rats. This TPT (12), unlike Old Tuberculin, has a high degree of antigenicity and its injection elicits precipitin antibodies.

Six normal rats were sensitized with the tuberculin protein fraction, TPT, by biweekly intracutaneous injections of 10 mg., each rat receiving 10 injections or a total of 100 mg. The first injection elicited no reaction; the next few were followed by small oedematous reactions. After the seventh to the tenth injection the reactions became more pronounced, resembling the tuberculin reactions in the rats previously described, but at no time was there any sign of induration or necrosis of these sites as seen in guinea pigs or rabbits.

The precipitin titre of the serum of these sensitized rats was 200,000, whereas in the normal rats it was only 2,000.

Longcope (13) obtained no skin reaction in white rats immunized against horse serum. In his animals the precipitin titre of the serum varied from 10 to 1,000. Opie (14) repeated this experiment on rats and failed to find any inflammatory oedema after intracutaneous injection of quantities of horse serum which produce the Arthus phenom-

enon in rabbits. Incision into the tissue at the site of injection failed to reveal any oedema. Among 4 rats which had received 15 injections of 1 cc. of horse serum at intervals of five or six days, precipitins were not demonstrable in the serum of one animal, and in 3 it reached a titre of 1,000 (trace). Opie therefore came to the conclusion that the intensity of the Arthus reaction in different species of animals varies; it may fail to occur in some (rat) and bears a close but not an exact relation to the ability of the animal to form precipitins.

This experiment confirms the work of Opie, for the tuberculoprotein (TPT) induces a mild skin reaction in the rat and is associated with a moderate precipitin titre in the blood. Thus it appears that both tuberculin sensitivity and tuberculoprotein sensitization of the Arthus type are feebly developed in the rat.

SUMMARY

1. Human, bovine and avian type tubercle bacilli, injected intravenously in the albino rat, induced tuberculous lesions in all the viscera except the kidney.

2. In different organs, lesions appeared at different stages of the disease; nodules appeared in the lungs within two weeks following infection with any of the three types of bacilli.

3. The gross lesions induced by the three types of bacilli were similar qualitatively, but the bovine type infection was more severe.

4. Caseation did not occur in any of the lesions.

5. Slight, atypical tuberculin sensitivity developed. Small swellings, without erythema or induration, appeared at the site of intracutaneous injection of tuberculin. Microscopically the mild reaction was predominantly mononuclear in its cellular character; no polymorphonuclear leucocytes were noted. Infected rats withstood large doses of tuberculin injected intraperitoneally, but 1 cc. of undiluted Old Tuberculin was occasionally fatal.

6. Rats repeatedly injected with tuberculoprotein failed to give evidence of more than slight sensitization. A typical Arthus phenomenon could not be induced, but precipitating antibodies were developed in slight degree.

7. The lack of symptoms of illness, the absence of sensitization to the products of the tubercle bacillus and the absence of caseation are probably correlated.

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TUBERCULOSIS IN THE RAT[1,2]

II. The Fate of Tubercle Bacilli in the Various Organs of the Rat

C. C. WESSELS

It has been shown by Lurie (1) that the cellular reaction in the various organs of a susceptible animal like the rabbit and the fate of the bacilli localized in them differ greatly after intravenous injection of tubercle bacilli of human and bovine types. From these studies the inference was drawn that the different organs in susceptible animals possess an inherently different power to destroy tubercle bacilli.

No studies along these lines have been made on as resistant an animal as the rat, and for this reason Doctor Lurie suggested that a similar endeavor be undertaken in this naturally resistant species, using living bacilli and correlating the fate of these, as measured by cultural methods, with the associated changes in the body.

METHOD

At varying intervals after intrajugular injection of varying doses of different types of tubercle bacilli, rats were killed by a blow on the head. The ventral surface of the animal, after removal of the hair, was thoroughly cleansed with an antiseptic and the skin then reflected with rigid precautions for sterility. The peritoneal cavity was opened with a separate sterile instrument for each step. The liver, which presented itself first, was removed, placed in a sterile Petri dish and accurately weighed. A small piece of the organ was then saved for histological studies; the remainder was again accurately weighed. In a similar way the spleen and kidneys were removed. The thoracic cavity was next opened, and in a similar manner the lungs and all the tracheobronchial lymph nodes were removed. All the above organs were then ground up separately in sterilized mortars with sterilized sand and suspended in a given quantity of fifteenth molar disodium phosphate (2). From these suspensions, containing a known weight of a given tissue, dilutions were made in the same alkaline medium. One cc. of each dilution of each tissue was shaken in a sterilized tube containing glass beads and seeded directly on three tubes of

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

[2] Presented in partial fulfillment for the degree of Doctor in Veterinary Medicine, University of Pennsylvania.

Dorset's medium and three tubes of modified Loewenstein's medium (3), divided as equally as possible and spread as evenly as possible on the surface of the medium by means of a sterile pipette. In order to have a uniform distribution of the material inoculated, the tubes were allowed to recline for half an hour, with the surface of the medium in a horizontal plane. The tubes were then incubated. Another 1 cc. specimen was treated with 6 per cent sulphuric acid, immersed in a water bath at 37°C. for half an hour, neutralized with disodium phosphate, centrifugalized and the sediment seeded as before. After the tubes had been left in the incubator for varying periods, the number of tubercle bacillus colonies in each was counted; this was repeated at weekly intervals. Since it was required that the tubes be kept in the incubator up to three months before the final readings were made, it was necessary to take precautions against drying of the medium. Also, to prevent spreading of colonies by the liquid of condensation, the tubes were always read in an upright position and handled as little as possible. If the number of colonies on the surface of the medium in a tube was not more than 200, they could easily be counted directly. When the colonies exceeded this number, they were estimated by wrapping about the tube a piece of thin metal foil from which square windows of varying sizes had been cut and reading these areas with a magnifying glass. Repeated readings eliminated gross errors. In cases of doubtful colonies, smears were made and stained by the Ziehl-Neelsen method.

Dosage: In one series of experiments, the fate of the three different types of tubercle bacilli, bovine, human and avian, as described in the first paper, was studied in the various organs of the rat, each infected with 0.1 mg. The rats were of approximately the same weight. In another series, the same procedure was carried out in rats infected with 0.001 mg. of the three strains.

The rats were killed twenty-four hours, one and two weeks, and one, two and three months after intrajugular injection.

All the rats used were pure-bred albino rats obtained from the Wistar Institute, Philadelphia. Intrajugular injection was carried out under ether anaesthesia when the vein was freed from surrounding tissues. After inoculation the wound was closed with sterile cotton sutures.

The figures in the tables represent the average number of colonies recovered, usually from six separate tubes of Dorset's and Loewenstein's media, each planted with the same quantity of the same suspension of tissue of a given dilution.

THE FATE OF BOVINE TYPE TUBERCLE BACILLI IN LARGE DOSAGES IN THE VARIOUS ORGANS OF THE RAT

In table 1 is recorded the number of colonies recovered from equal weights of liver, spleen, kidney, lung and tracheobronchial lymph nodes, one day, one week, two weeks, one month, two months and three months

after injection of 0.1 mg. bovine type tubercle bacilli of the Ravenel strain, into rats, after direct seeding upon Dorset's and Loewenstein's media following four months' incubation. The curves plotted in chart

TABLE 1

Number of colonies obtained from 10 mg. of organs of rats infected with 0.1 mg. M. tuberculosis, bovine type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL NODE
		Direct, Dorset and Loewenstein				
R 1	24 hours	6,781	5,025	608	4,047	1,950
R 7	24 hours	6,460	5,250	59	5,193	20
Average.....	24 hours	6,620	5,137	333	4,620	985
R 2	1 week	94,300	41,880	969	20,530	7,600
R 8	1 week	52,290	88,080	746	251,200	56,650
Average.....	1 week	73,295	64,980	857	135,865	32,125
R 3	2 weeks	15,682	80,570	2,573	485,000	1,430
R 9	2 weeks	67,100	130,500	974	280,100	29,850
Average.....	2 weeks	41,391	105,535	1,773	382,550	15,640
R 4	1 month	4,500	5,000	54	1,023,000	2,980
R 10	1 month	16,100	12,800	90	420,000	7,000
Average.....	1 month	10,300	8,900	72	721,500	4,990
R 5	2 months	3,540	29,860	184	370,000	800
R 11	2 months	2,020	17,400	3,123	1,060,000	7,900
Average.....	2 months	2,780	23,630	1,653	715,000	4,350
R 6	3 months	1,957	19,680	1,011	110,000	7,660
R 12	3 months	350	5,960	8	71,000	1,500
Average.....	3 months	1,153	12,820	509	90,500	4,580

I show the arithmetical averages of the number of bacilli recovered from each organ of two separate rats.

As could be expected, the number of colonies recovered from both media after sulphuric acid treatment was smaller. However, as these results were essentially parallel to those obtained on direct seeding and

since we are concerned with the relative and not with absolute quantities, these data are omitted. Actually tubercle bacilli were isolated without treatment in pure culture from the various organs in practically all cases.

Original deposition: Twenty-four hours after the intravenous injection of bacilli the number of colonies recovered from 10 mg. of the various organs was as follows: The liver revealed an average of 6,620 colonies,

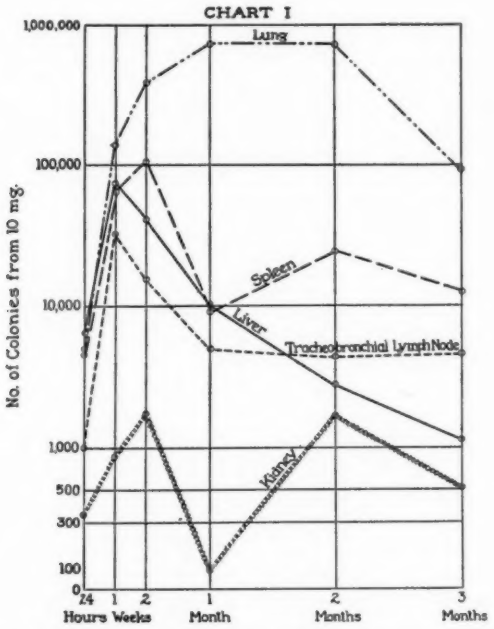

CHART I. The fate of bovine type tubercle bacilli in large dosage, 0.1 mg., in the various organs of the rat.

the spleen, 5,137, the lung, 4,620, the tracheobronchial lymph nodes, 985 and the kidney, 333 colonies.

One week after infection there was a rapid multiplication of the bacilli in the different organs, although not to the same degree in all. The lung showed the most rapid increase, then the spleen, next the liver and then the tracheobronchial lymph nodes; the kidney showed the least rapid multiplication of the microörganism.

During the second week the multiplication of bacilli in the lung, spleen and kidney continued, although it was not nearly as rapid as during the

first week. On the other hand, in the liver and tracheobronchial lymph nodes there was a diminution of the bacilli.

During the interval between two weeks and one month after infection, a striking difference occurred between the lung, on the one hand, and the liver, spleen, kidney and tracheobronchial lymph nodes on the other. In the lung, during this interval, there was still unabated multiplication of the bacilli, although it was less intense than during the first two weeks. In the other organs during this interval there was definite reduction of the bacilli.

During the interval between the first and second month there was a cessation of multiplication of bacilli in the lung. At this stage the number of bacilli in the tracheobronchial lymph nodes remained unchanged, but in the liver there was still continued destruction of bacilli. On the other hand, the spleen again showed a slight rise, and in the kidney a definite increase in their numbers took place.

At the end of three months, the microörganisms continued to decrease in almost all the organs; in the tracheobronchial lymph nodes, however, their numbers were undiminished.

It is noteworthy that at this stage, although destruction of bacilli had taken place in most of the organs, it was far from complete. Except for the liver, in which the number of bacilli had reached a level definitely below the original deposition, in all the other organs, despite the early onset of destruction, the numbers of bacilli were still higher than the original localization in those organs, and, the lung excepted, were undiminished from the levels reached at the end of the first month.

It is apparent, therefore, that during the first week after infection with 0.1 mg. bovine type tubercle bacilli, there is multiplication of bacilli in all the organs, and this multiplication continues unabated during the second week, except in the liver and tracheobronchial lymph nodes, in which definite destruction of the bacilli occurs. Furthermore, at the end of the first month, destruction of bacilli becomes apparent in all the organs except in the lung, where multiplication of bacilli continues. Cessation of multiplication becomes apparent here at the end of the second month and definite diminution of their numbers does not occur until the end of the third month. Even at this time, 90,000 colonies could still be recovered from 10 mg. of lung. It is noteworthy that the lungs, which show the most rapid original multiplication of the bacilli, also destroy them least during the course of the disease.

THE FATE OF HUMAN TYPE TUBERCLE BACILLI IN LARGE DOSAGE IN THE VARIOUS ORGANS OF THE RAT

Table 2 and chart II show the fate of human type tubercle bacilli in the various organs of the rat at different intervals of time after the intrajugular injection of 0.1 mg. of the human type, strain P 15 B.

TABLE 2

Number of colonies obtained from 10 mg. of organs of rats infected with 0.1 mg. M. tuberculosis, human type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL LYMPH NODE
		Direct, Dorset and Loewenstein				
R 25	24 hours	20,470	8,770	397	12,340	740
R 26	2 weeks	3,866	14,430	46	189,900	11,630
R 27	2 months	220	1,140	86	7,800	430

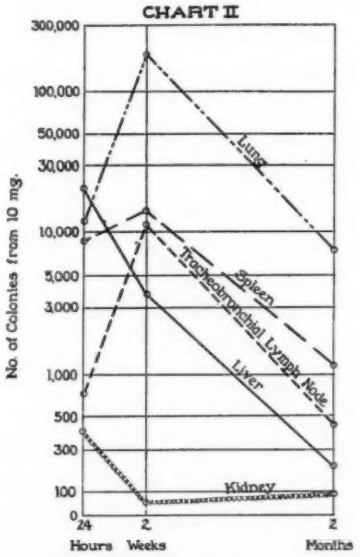

CHART II. The fate of human type tubercle bacilli in large dosage, 0.1 mg., in the various organs of the rat.

More colonies were cultured one day after inoculation from equal quantities of lung, liver and spleen of rats infected with the human type bacillus than from the same amounts of tissue of rats similarly infected with the bovine type bacillus. Considerable multiplication took place

in the lung, tracheobronchial nodes and spleen during the first two weeks of the infection. After this period a marked difference occurred between the human and bovine infections in that in the case of the human infection the destruction of the tubercle bacillus was much more rapid and extensive than in the case of the bovine infection. At the end of two months this difference was especially pronounced in the lung, in which, with the bovine infection, there was only a cessation of multiplication, whereas in the case of the human infection the destruction was so effective that the number of colonies had come down to a level very much below that of the original deposition. Again it is noteworthy that the liver is the least advantageous location for the bacilli. No multiplication of human type bacilli was noted in this organ. It was in the liver that the first destruction of the microörganism of bovine infected tissues took place.

TABLE 3

Number of colonies obtained from 10 mg. of organs of rats infected with 0.1 mg. M. tuberculosis, avian type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL LYMPH NODE
		Direct, Dorset and Loewenstein				
R 31	24 hours	27,920	15,840	544	15,380	90
R 32	2 weeks	28,890	24,000	77	21,500	13,850

THE FATE OF AVIAN TYPE TUBERCLE BACILLI IN LARGE DOSAGES IN THE VARIOUS ORGANS OF THE RAT

Table 3 shows the fate of avian type tubercle bacilli in the various organs of the rat at different intervals of time, after the intrajugular injection of 0.1 mg. of bacilli of the strain Avian 12.

Unfortunately, as a result of an intercurrent disease, the rat which was to be cultured after two months' infection died.

Here again, twenty-four hours after infection, the relative distribution of the microörganisms in the various organs is comparable to that of the bovine infection; namely, most were found in the liver, with the spleen and lungs following in the order named. More avian type tubercle bacilli were recovered from the organs at this time than from organs similarly infected with bovine or human type bacilli.

After two weeks, the multiplication of the avian bacilli in the lung

was very slight compared to that in the case of bovine and human type infections.

THE FATE OF BOVINE TYPE TUBERCLE BACILLI IN SMALL DOSAGE IN THE VARIOUS ORGANS OF THE RAT

Table 4 and chart III show the fate of bovine type tubercle bacilli in the various organs of the rat at different intervals of time after the

TABLE 4

Number of colonies obtained from 10 mg. of organs of rats infected with 0.001 mg. M. tuberculosis, bovine type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL NODE
		Direct, Dorset and Loewenstein				
R 13	24 hours	98	45	1	37	0
R 19	24 hours	255	98	5	92	0
Average.....	24 hours	176	71	3	64	0
R 20	1 week	2,964	3,749	11	3,767	1,930
R 15	2 weeks	537	3,534	1	130	2,070
R 21	2 weeks	2,050	6,330	4	14,260	13,520
Average.....	2 weeks	1,293	4,932	2	7,195	7,795
R 16	1 month	320	6,240	5	51,200	5,230
R 22	1 month	721	8,690	23	32,200	7,870
Average.....	1 month	520	7,465	14	41,700	6,550
R 17	2 months	40	6,370	4	20,000	1,190
R 23	2 months	173	823	1	54,100	990
Average.....	2 months	106	3,596	2	37,050	1,090
R 18	3 months	21	3,433	1	81,100	540
R 24	3 months	688	11,610	15	92,600	3,030
Average.....	3 months	354	7,521	8	86,850	1,785

intrajugular injection of 0.001 mg. of the Ravenel strain. Twenty-four hours after infection the relative distribution was the same as with the larger dose of bovine type tubercle bacilli. One week after infection

there was a definite multiplication in all the organs, and the rate of multiplication in the lung and spleen ran parallel. Two weeks after infection, as with the larger dose, there was still multiplication of the organisms in the lung and spleen, although the multiplication was not as rapid as during the first week. On the other hand in the liver, as with the larger dose, there was definite destruction of the tubercle bacillus. One month after infection, unlike the result found with the larger dose, there was still active multiplication of the bacilli in the spleen. Two months after infection a definite reduction of the bacilli had taken place in all the organs.

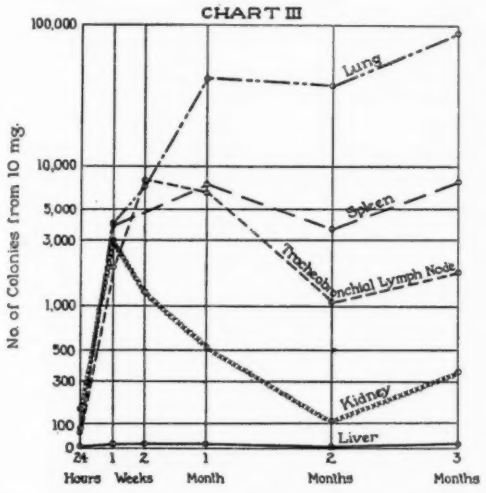

CHART III. The fate of bovine type tubercle bacilli in small dosage, 0.001 mg., in the various organs of the rat.

A very striking difference between the small and large dosage was apparent at the two and three month intervals after infection; secondary active multiplication of the bacilli in all the organs was apparent in the rats infected with the small dosage, while at this time definite destruction of the bacilli was taking place in all the organs in rats infected with the larger dose.

THE FATE OF HUMAN TYPE TUBERCLE BACILLI IN SMALL DOSAGE IN THE VARIOUS ORGANS OF THE RAT

Table 5 and chart IV show the fate of human type tubercle bacilli in the various organs of the rat at different intervals of time after the

intrajugular injection of 0.001 mg. of the human type, strain P 15 B.

With the small as with the larger dosage, twenty-four hours after infection more tubercle bacilli were isolated from the lungs of the rat infected with the human than from the lungs of rats infected with the bovine strain. After two weeks there was a marked rise in the number of colonies recovered from the spleen and lung, but at this stage, as with

TABLE 5

Number of colonies obtained from 10 mg. of organs of rats infected with 0.001 mg. M. tuberculosis, human type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL LYMPH NODE
		Direct, Dorset and Loewenstein				
R 28	24 hours	114	60	3	470	10
R 29	2 weeks	32	1,496	3	1,540	270
R 30	2 months	1	30	0	2,220	200

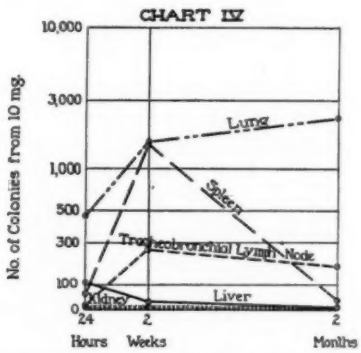

CHART IV. The fate of human type tubercle bacilli in small dosage, 0.001 mg., in the various organs of the rat.

the smaller dosage of bovine infection, the liver showed destruction of the bacilli.

After two months, as with the small dosage of bovine type bacilli, there was considerable destruction of the bacilli, except in the lung, where there was still unabated growth. However, at this stage it is noteworthy that, in spite of the fact that the original number of colonies recovered from the different organs twenty-four hours after infection was about the same in both the human and bovine infections, yet after two months

the destruction of the human type tubercle bacilli was much more extensive in all the organs than in the case of the bovine infection.

THE FATE OF AVIAN TYPE TUBERCLE BACILLI IN SMALL DOSAGE IN THE VARIOUS ORGANS OF THE RAT

Table 6 and chart V show the fate of avian type tubercle bacilli in the various organs of the rat at different intervals of time after the intrajugular injection of 0.001 mg. of Avian 12.

TABLE 6

Number of colonies obtained from 10 mg. of organs of rats infected with 0.001 mg. M. tuberculosis, avian type

RAT NUMBER	INTERVAL AFTER INJECTION	LIVER	SPLEEN	KIDNEY	LUNG	TRACHEO-BRONCHIAL LYMPH NODE
		Direct, Dorset and Loewenstein				
R 34	24 hours	154	43	2	46	0
R 35	2 weeks	2,032	2,966	2	185	20
R 36	2 months	350	1,101	0	110	1,160

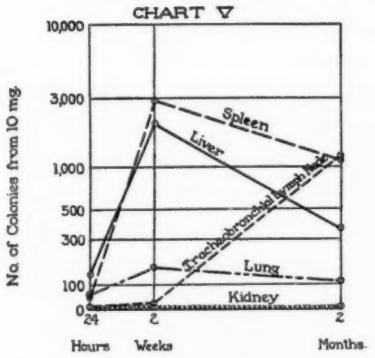

CHART V. The fate of avian type tubercle bacilli in small dosage, 0.001 mg., in the various organs of the rat.

Twenty-four hours after injection, the number of colonies recovered from the various organs closely approximated that recovered from the same organs after a similar dosage of bovine type tubercle bacilli. The number, except in the lung, also approximated that recovered from the various organs after a small dosage infection with human type tubercle bacilli. Two weeks after infection the behavior of the liver and spleen toward the avian type bacilli was very much like that found in the case

of the small dosage of bovine infection; *i.e.*, there was a marked multiplication of the bacilli. On the other hand, in contradistinction to the bovine and human infections, the number of colonies recovered from the lung in the case of the avian infection showed only a slight increase.

Two months after infection, although marked destruction of bacilli had taken place in the spleen and liver, yet, as with the bovine infection, the destruction of the bacilli in these two organs was not nearly as extensive as in the case of the human type infection. On the other hand, in the avian infection, the behavior of the lung toward the bacilli was quite different from that in the case of either the human or the bovine infection, as can be seen from the very small numbers of colonies isolated at the varying intervals of time after infection.

DISCUSSION

In summarizing the results obtained by cultural methods it may be said that the original deposition of mammalian and avian type tubercle bacilli in the various organs of the rat corresponds with the distribution of particulate matter (4, 5). In the majority of instances the deposition was greatest in the liver, decreasing, in order, in the spleen, the lung and tracheobronchial lymph nodes, and was least in the kidney. Occasionally with a small dose the lung filtered out the greatest number of microorganisms.

These results confirm the findings of Lurie (6) with this exception, that in his studies on the rabbit the original deposition of bacilli was greatest in the spleen, next in the liver and then in the lung.

The fate of the bacilli after the original deposition depends upon many factors, including the type of bacillus, whether mammalian or avian, the dosage and undoubtedly many other conditions such as individual susceptibility and resistance.

It is apparent that at first there is multiplication of the tubercle bacillus in all the organs. The rate of multiplication of the three different types is very different in the various organs. Thus, in most cases with the two mammalian strains, the multiplication is more rapid in the lung than in the other organs, while on the other hand, with the avian strain the spleen shows a more rapid multiplication than the lungs. But in the early stage in all the organs there is no effective opposition to the multiplication of the tubercle bacillus.

Soon, however, a striking change takes place. Destruction of the tubercle bacilli starts in the different organs, but the time at which the

destruction begins depends on the dose and type of infection. Thus, with the large dosage of bovine type infection the liver and tracheobronchial lymph nodes show destruction of the bacilli at the end of the second week, when there is still active multiplication of bacilli in the lung and spleen. In the latter, destruction is evident at the end of the first month; in the lung, destruction becomes apparent only at the end of three months. With the smaller dosage of bovine bacilli, destruction of the microörganism in the tracheobronchial lymph nodes does not become evident until the first month, and a secondary multiplication is noted in all the organs between the second and third months.

Lurie (7), in his studies on the rabbit, has shown that the human type tubercle bacillus grows much faster than the bovine type, but that destruction of the human type begins at a time when the bovine type bacilli have reached their highest numbers; the latter's destruction becomes apparent only at a later interval. He has shown further that associated with this more rapid initial multiplication of the human type, its destruction at a given time is much more extensive than is that of the more slowly growing bovine type.

In these experiments, unfortunately, rats infected with the human type could not be cultured one week after infection and only one rat was used for each interval. It is impossible, therefore, to state whether in these experiments the initial multiplication after infection with the human type was faster than that with the bovine type. It has been seen that twenty-four hours after infection the numbers of bacilli of the human type recovered from the liver, lung and spleen are much higher than those cultured from rats infected with the bovine type. Yet, after two weeks in the case of the bovine infection the numbers of bacilli recovered from the liver, spleen and lung were 41,391, 105,535 and 382,550, respectively, whereas in the case of the human type after two weeks' infection the numbers are only 3,866, 14,430 and 189,900, respectively, proving that in the human type of infection the destruction is much more extensive. After two months this observation is still more evident, as can be seen in tables 1 and 2 and charts I and II. This confirms Lurie's finding (7) that, at a given time after infection, the destruction of the human type tubercle bacillus is much more extensive than is that of the bovine type. This observation holds true also for the small dosage infection, as indicated by tables 4 and 5 and charts III and IV.

Further, it is apparent that two months after infection with the small

dosage of bovine type, the destruction is less extensive than in the case of a similar dosage of human type. Also after two months' infection with the larger dosage of human type tubercle bacilli, the destruction is more extensive and complete than after two months' infection with the smaller dosage of human type. Again in the bovine type, after three months' infection, the destruction of bacilli is more extensive and complete with the larger dosage than with the smaller one.

From the above it is evident that, as with the susceptible animal, the fate of the bacilli in the various organs differs greatly (1). From these studies the inference is drawn that the different organs in a resistant animal like the albino rat possess an inherently different power to destroy tubercle bacilli.

It is therefore apparent that the difference in the behavior of these two animals toward the tubercle bacillus is partly quantitative rather than qualitative. Further, although these studies confirm the findings of Lurie (7), the difference of the host response to the organism is clearly reflected in the following two points.

First, certain organs of the rabbit have a much greater capacity to destroy the tubercle bacillus than the same organs of the rat. This is especially noted in the liver and spleen of the rabbit (7), where after two months of infection the destruction is almost complete. On the other hand the lungs and kidneys, which are the susceptible organs in the rabbit, do not destroy the bacilli at all in the case of a bovine infection, while in the case of human type infection the destruction is only partial. These organs eventually become greatly involved by the tuberculous changes with the usual development of caseation and softening (7).

In the rat, however, although destruction of the bacilli also takes place in all the organs, it does not occur to the same extent as in the organs of the rabbit. Even in the liver and spleen the destruction of the bacilli is much less extensive than in the corresponding organs of the rabbit (8). In the rat also, the lung is the susceptible organ and the destruction of the bacilli in this organ is much less extensive than in the other organs and, in consequence, the lung becomes greatly involved by the tuberculous process.

Secondly, in the rabbit, the disease pursues a progressive course, with the development of caseation and results in the death of the animal, while in the rat, although the disease also progresses in the lung, at no stage of the disease are there any signs of caseation. Also, in spite of the fact that large numbers of bacilli can be recovered from most of the

organs, yet at no time do any of the infected rats reveal any clinical symptoms of the disease, while the rabbit is obviously intoxicated by the virulent bovine infection.

With avian type tubercle bacilli after intrajugular injection in the rat, it appears as if the disease takes a different course. Here the lung has a much greater capacity for destroying the bacilli than either the spleen or liver, and, in contradistinction to the bovine and human types of infection, the avian type bacilli in the rat's liver and spleen persist.

SUMMARY

1. In the rat, after intravenous injection of mammalian and avian type tubercle bacilli, the deposition of the organisms in the various organs corresponds with the distribution of particulate matter, and is generally found to be in the following decreasing order, liver, lung, spleen, tracheobronchial lymph nodes and kidney.

2. Both mammalian and avian type tubercle bacilli, after infection, multiply in all the organs without any effective opposition.

3. The rate of multiplication of mammalian and avian types differs in the various organs. With the bovine and human types it is most rapid in the lung, while with the avian type it is fastest in the spleen.

4. In the case of bovine type infection, the destruction of the microorganisms in the various organs is less extensive than in the case of human type infection.

5. In both bovine and human types of infection, destruction of the microörganism occurs first in the liver. In the lung, the human type is being destroyed while unabated growth of the bovine type still takes place.

6. With both bovine and human types, destruction of bacilli is more extensive in most of the organs after a large dosage than after a small one.

7. With the bovine type, the growth of the microörganisms in most of the organs is at first very rapid and then slower. Again, destruction in most of the organs is rapid at first, but, as time passes, becomes slower, so that three months after infection with varying dosages, large numbers of bacilli can still be recovered from all the organs.

8. With the avian type, the liver and spleen do not destroy the microorganisms to the same extent as is the case with the mammalian types, but, on the other hand, in the lung the destruction is much more extensive than in the mammalian types of infection.

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ARTIFICIAL PNEUMOTHORAX IN PATIENTS OVER FORTY[1, 2]

SIDNEY DIAMOND AND HUBERT T. IVEY

Of all the collapse therapy measures employed to-day in our efforts to effect the closure of tuberculous cavities, artificial pneumothorax is the one used most frequently. Therapeutic pneumothorax has been induced in patients of all ages from infancy to the eighth decade. Inasmuch as pulmonary tuberculosis is principally a disease of adolescents and young adults, however, the procedure has found its greatest application in the treatment of patients between the ages of fifteen and thirty-five. Extensive studies of the results and complications attending its use in this age group have made us thoroughly familiar with the efficacy of artificial pneumothorax in young persons. Comparatively little work has been done in estimating the value of the procedure in persons further along in years. As a result, our actual knowledge of the precise merits of pneumothorax therapy in persons of middle age is still meagre.

In an attempt to evaluate the worth of artificial pneumothorax in older persons, we made a survey of 431 white World War veterans in whom pneumothorax was instituted or attempted after they had passed their fortieth birthday. This study covered the five-year period which began January 1, 1935 and ended January 1, 1940. The actual number of patients over forty treated by pneumothorax during this period in the two hospitals from which our material was drawn was considerably larger than the number in our series, but the data in many of the cases were too inadequate to warrant their inclusion in our study. In 25 of our patients, efforts were made to establish bilateral pneumothoraces. In view of the fact that each diseased lung presents an independent problem as far as collapse therapy is concerned, we deemed it advisable to consider each lung subjected to artificial pneumothorax as a separate case. Our series,

[1] From the Tuberculosis Services, Veterans Administration Facilities, Tuscon, Arizona and Legion, Texas.

[2] Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the authors.

therefore, embraced 456 cases, or pneumothorax sides, although it included only 431 patients.

Every one of our patients had a positive sputum and a roentgenographically demonstrable cavity at the inauguration of his collapse therapy program. Of the 431 patients, 349 (81 per cent) had far advanced disease; 82 (19 per cent) had moderately advanced lesions. The disease process was unilateral in 212 (49.3 per cent), bilateral in 219 (50.7 per cent). Sixty patients (14 per cent) had at least one cavity whose diameter exceeded 4 cm. The average age of the patients was slightly under forty-four years; 30 patients (7 per cent) were over fifty years of age, the oldest being fifty-eight. The duration of the patients' tuberculosis prior to the attempted induction of pneumothorax ranged from one month to eighteen years; 210 patients (44 per cent) had been ill less than one year; the length of the average history was three years and ten and one-half months.

RESULTS

We divided the results obtained in our series into three categories. Patients with apparently permanent closure of the cavities and conversion of the sputa were classed as successful. Those in whom the desired therapeutic effect was not attained, despite the establishment of a pneumothorax space, were designated as unsuccessful. Those in whom separation of the pleural surfaces could not be effected were listed as impossible. The criteria for our calling a case successful were roentgenographic evidence of cavity closure and failure to demonstrate tubercle bacilli in concentrated sputa for a period of six consecutive months.

Table 1 shows the relative number of successful, unsuccessful and impossible pneumothoraces in the 456 cases attempted. The average age of the patients in the successful group was approximately two years less than the average age of the others. The proportion of successful pneumothoraces in our series was greater than the 11.5 per cent reported by Decker (1) in 78 patients over forty, but was somewhat smaller than that generally observed in younger patients. Figures recorded by various authors differ markedly, depending on the selection of cases, the standards for classing a collapse as successful and numerous other factors; the average proportion of successful pneumothoraces in persons of all ages in the stages of disease comparable to those of our patients appears to be approximately 35 to 40 per cent. Tice and Hruby (2), in reviewing 679 pneumothorax cases in which the age of the majority of the

patients was below forty, found 40 per cent of the cases successful. Matson, Matson and Bisaillon (3) obtained a satisfactory collapse in 39 per cent of 600 cases. On the other hand, Johnston (4) described only 22 per cent of the cases in his series as successful.

Complete pleural symphysis was encountered among our patients with slightly greater frequency than that with which it has been found in younger patients. Matson, Matson and Bisaillon (3) found pneumothorax impossible in 20 per cent of their cases, Kendall (5) in 25 per cent, Bronfin (6) and Swezey and Schonbar (7) in 26 per cent. In Heaton's (8) series of 3,381 cases, the pleural surfaces were inseparable in 27 per cent.

The effectiveness of the collapse bore a direct relationship to the brevity of the disease history antedating the inception of pneumothorax. Of the patients who had been ill less than six months, pneumothorax

TABLE 1

Proportion of successful pneumothoraces

	NUMBER	PER CENT	PATIENTS' AVERAGE AGE IN YEARS
Successful	92	20.2	42.4
Unsuccessful	222	48.7	44.3
Impossible	142	31.1	44.4
Totals	456	100	43.9

was successful in 26.6 per cent. Of those ill less than one year, it was successful in 22.4 per cent. Of those whose history exceeded one year, it was successful in only 18.1 per cent. These figures lend support to the view held by virtually all phthisiologists that the earlier pneumothorax is begun the better are the chances for its success.

The stage of the patient's disease appeared to be a major factor in the effectiveness of the collapse. Pneumothorax was successful in 26.8 per cent of patients whose tuberculosis was only moderately advanced, whereas in those in whom the lesion was more extensive it was effective in but 18.6 per cent. These findings are in accord with the observations of most other investigators. The experience of Turner and Collins (9) in a series of 45 minimal cases, in which pneumothorax was successful in 100 per cent, offers the most striking example of the relation between the extent of the disease process and the efficacy of the collapse obtained.

In our efforts to estimate the rapidity of cavity closure and sputum

conversion in the successful cases, we limited our study to the 70 strictly unilateral cases in which pneumothorax was effective alone, without the aid of accessory surgical procedures. In bilateral cases there was no way of accurately gauging the actual success of the pneumothorax until the sputum had been turned negative by adequate collapse of the contralateral side. In the 70 patients studied, effective collapse was obtained in 11.4 per cent in less than three months, 21.4 per cent in three to six months and 54.3 per cent in six to twelve months. Thus, 87.1 per cent of the pneumothoraces became successful in less than a year. The average conversion time was nine months. It has been clearly demonstrated by numerous investigators that there is a direct relationship between the age of the patient and the length of time required for closure of the cavity by artificial pneumothorax. In Siegel and Singer's (10) series of children from five to fifteen years of age, all of the patients became sputum-negative within six months. Bendove (11) and his collaborators reviewed a group of patients ranging in age from sixteen to twenty-five years and found that sputum conversion was attained in 95 per cent within the same period. In a survey of cases including patients of all ages, with those under forty predominating, Tice and Hruby (2) observed success in 39 per cent within three months and in 69 per cent within six months. Similarly, Eglee and Jones (12) noted sputum conversion in 39 and in 60 per cent within the corresponding periods. The observations of Bendove (11) and his associates in patients aged thirty-five to forty-five closely parallel ours: 11.6 per cent of the cases successful in three months and 20.1 per cent in three to six months.

There appeared to be a definite correlation between the time interval of sputum conversion and the length of the previous history of disease, but no significant relationship between the time interval of sputum conversion and the extent of the disease process. In table 2 we see that approximately half of the patients who had had tuberculosis less than a year became sputum-negative within the first six months of treatment, whereas 85 per cent of those who had been ill longer than a year did not become sputum-negative until the pneumothorax had been maintained for a period longer than six months. That the anatomical extent of the pulmonary lesion had little bearing on the rapidity of cavity closure is illustrated by the figures in table 3. The proportion of far advanced cases in which pneumothorax was successful in the various time intervals differed but slightly from that of the moderately advanced cases in the corresponding intervals.

The simultaneous application of artificial pneumothorax to both lungs was undertaken in 25 of our patients. It was successful in 5. In 10 patients it was effective on one side, unsuccessful or impossible on the other. In these 10 patients the disease in the contralateral lung was controlled by other means; by extrapleural pneumothorax in 4 and by

TABLE 2

Relation of length of history of tuberculosis to rapidity of cavity closure and sputum conversion in successful cases

DURATION OF PNEUMOTHORAX BEFORE CLOSURE OF CAVITY AND CONVERSION OF SPUTUM	LENGTH OF DISEASE HISTORY	
	Less than 1 year	More than 1 year
Less than 3 months	6 (16.2%)	2 (6.0%)
3 to 6 months	12 (32.2%)	3 (9.1%)
6 to 12 months	15 (40.5%)	23 (69.7%)
Less than 1 year	33 (88.9%)	28 (84.8%)
More than 1 year	4 (11.1%)	5 (15.2%)
Totals	37	33

TABLE 3

Relation of stage of disease to rapidity of cavity closure and sputum conversion in successful cases

DURATION OF PNEUMOTHORAX BEFORE CLOSURE OF CAVITY AND CONVERSION OF SPUTUM	MODERATELY ADVANCED	FAR ADVANCED
Less than 6 months	6 (33.7%)	17 (32.7%)
6 to 12 months	12 (66.7%)	26 (50.0%)
Less than 1 year	18 (100%)	43 (82.7%)
Totals	18	52

thoracoplasty in 6. The ratio of successful bilateral pneumothoraces to the number attempted, therefore, was virtually identical with that found in the unilateral cases. These findings offer no basis for the general disfavor with which most observers look upon bilateral pneumothorax as a therapeutic agent in older persons; Carman (14), for instance,

states that if the patient is more than forty years of age a definite contraindication to bilateral pneumothorax exists.

Complemental procedures for the conversion of unsuccessful pneumothoraces into successful ones included intrapleural pneumonolysis, crushing of the ipsolateral phrenic nerve and simultaneous extrapleural pneumothorax. Thoracoscopy was performed in 51 (23 per cent) of the 314 pneumothorax cases and in 20 of these cases division of the offending adhesions led to closure of the cavities. Thus, in 21.7 per cent of our successful cases, adequate collapse was obtained only after one or more adhesions had been severed. The literature reflects a wide divergence of opinion among phthisiologists regarding the indications for pneumonolysis. At one extreme is Matson (13), who maintains that intrapleural pneumonolysis will convert 70 per cent of unsatisfactory pneumothorax cases into satisfactory ones; he bases his observation on results obtained in a series of more than 1,500 pneumothoraces. At the other extreme is Bronfin (6), who has found clear-cut indications for pneumonolysis in only 3 per cent of his pneumothorax cases.

Crushing of the ipsolateral phrenic nerve was employed in 29 of our pneumothorax cases. In only one case was the operation followed by closure of the cavity. If we may digress for a moment, it is interesting to note that in 18 of our impossible cases the phrenic nerve was crushed with but one clinically successful result. Thus, the procedure was resorted to in a total of 47 (10.3 per cent) of our 456 cases; in only 2 of the cases (4.3 per cent) did it prove effective. Our findings in this regard are at considerable variance with the observation of Decker (1) that phrenic nerve operations show the best returns of all the collapse therapy methods in patients over forty.

In one of our patients who had a far advanced bilateral lesion, intrapleural pneumothorax appeared to be effective in closing the cavities in the middle and lower thirds of the lung on one side. One cavity in the apex, however, was kept open by dense pleural adhesions which could not be severed intrapleurally. An extrapleural pneumothorax therefore was created on this side and maintained with refills, in an effort to collapse the apical cavity; at a later date, it was hoped, the band of parietal pleura, separating the two pneumothorax spaces, would be cut and the two spaces united. The procedure failed to accomplish the desired purpose, however, and ultimately both the intrapleural and the extrapleural pneumothoraces were discontinued.

In none of our patients was it necessary to abandon a successful pneu-

mothorax because of undue dyspnoea caused by its maintenance. Most of the successful cases were followed by us for at least a year after the time of sputum conversion, some for as long as four years. In no instance was any evidence of reactivation of the disease in the collapsed lung noted. Three patients in the successful group died during the five-year period. An intercurrent disease was the cause of death in each of the three. One of the patients died from a coronary occlusion, another from a carcinoma of the maxillary antrum and the third from an acute exacerbation of chronic glomerulonephritis, with uraemia.

COMPLICATIONS

The development of fluid within the pneumothorax cavity is unquestionably the most common complication of artificial pneumothorax. It is apparent from the figures cited in the literature that considerable disagreement prevails in regard to the actual incidence of this complication. Burrell (15) and Matson, Matson and Bisaillon (3) voice the belief that intrapleural fluid is present at some time or other in the course of every artificial pneumothorax. Cutler (16) has observed it in over 90 per cent of pneumothorax cases, Weisman (17) in 84 per cent, Hayes (18) in 82 per cent, Rosenthal (19) in 76 per cent, Coryllos (20) in over 60 per cent, Brock, Mullen and Woodson (21) in 60 per cent and Mayer and Dworkin (22) in 50 per cent. On the other hand, DeCecio and Potter (23) have found it in only 34 per cent, Franklin, Zavod and Perez (24) in 30 per cent and Kendall (5) in 29 per cent. In a group of children receiving pneumothorax therapy, Siegel and Singer (10) have noted pleural effusions in 70 per cent. It is likely that the remarkable disparity in these statistics is due, in part at least, to differences in the type of cases treated by pneumothorax, variations in the diligence with which insignificant transitory effusions have been looked for and the failure of a number of the authors to include cases in which the fluid has been confined to the costophrenic sinus.

In our series, intrapleural fluid was noted in 268 (85.6 per cent) of the 314 pneumothorax cases. This number comprised all effusions observed, irrespective of their size or nature or the length of time they remained in the pleural space; it included instances in which a tiny costophrenic puddle made its appearance at but a single fluoroscopy. In 127 (40.3 per cent) of our pneumothorax cases the quantity of fluid present was sufficient to completely cover the diaphragm. Empyema (we use the term to designate an opaque, purulent effusion, regardless of its bacterial

content) developed in 32 cases, which constituted 25 per cent of the cases with significant supradiaphragmatic effusions and 10.2 per cent of the total number of pneumothorax cases.

Comparing the proportion of effusions of all kinds in the unsuccessful and the successful pneumothoraces (table 4), we find that 12.2 per cent of the unsuccessful cases developed empyemata, whereas that complication occurred in only 5.4 per cent of the successful cases. Otherwise there were no significant differences. It will be noted that tiny costophrenic effusions appeared in a somewhat smaller percentage of unsuccessful cases than successful cases. This, however, was in all likelihood due to the fact that many obviously unsuccessful pneumothoraces were abandoned after only short periods of treatment; had they been con-

TABLE 4

Proportion of pneumothorax cases developing pleural effusions

	NUMBER OF PNEUMOTHORAX CASES	FLUID IN COSTOPHRENIC SINUS	FLUID ABOVE DIAPHRAGM	EMPYEMA
Successful	92	82 (89.1%)	37 (40.2%)	5 (5.4%)
Unsuccessful	222	186 (83.0%)	90 (40.5%)	27 (12.2%)
Totals	314	268 (85.6%)	127 (40.3%)	32 (10.2%)

tinued for longer periods, fluid probably would have developed in a number of the cases.

The majority of the effusions in our series appeared early in the course of collapse therapy. Of the total number, approximately 61 per cent were present within three months of the inception of pneumothorax, 86 per cent within six months and 98 per cent within a year. Of the effusions which covered the diaphragm, 37 per cent developed in the first three months, an additional 27.6 per cent appeared in the following three months and by the end of the first year, 86.6 per cent had formed. Our findings in this respect parallel those of other investigators. Mayer and Dworkin (22) observed that 50 per cent of their effusions developed in the first two months of treatment and 90 per cent in the first half-year. Weisman (17) found 75 per cent present in the first six months and 91 per cent in the first year. In Burrell's (15) series, which included only effusions of considerable size, 33 per cent made their appearance within

three months, 65 per cent within six months and 88 per cent within a year.

Our efforts to determine the relation between the length of the tuberculosis history and the tendency to the development of fluid during pneumothorax therapy brought to light a highly interesting and significant point, which is clearly illustrated by the figures in table 5. The duration of the disease appeared to bear little or no relation to the formation of costophrenic effusions. However, of those patients who had been ill less than six months at the time their pneumothoraces were begun, a disproportionate number subsequently developed larger effusions and empyemata. Apparently, the more acute the disease process

TABLE 5

Relation of length of history of tuberculosis to development of pleural effusion

LENGTH OF DISEASE HISTORY	NUMBER OF PNEUMOTHORAX CASES	FLUID IN COSTOPHRENIC SINUS	FLUID ABOVE DIAPHRAGM	EMPYEMA
Less than 6 months.....	78	68 (87.2%)	48 (61.5%)	12 (15.4%)
6 to 12 months.....	40	35 (87.5%)	15 (37.5%)	3 (7.5%)
Less than 1 year.....	118	103 (87.3%)	63 (53.4%)	15 (12.7%)
More than 1 year.....	196	165 (84.2%)	64 (32.7%)	17 (8.7%)
Totals.....	314	268 (85.6%)	127 (40.3%)	32 (10.2%)

in the lung the greater was the likelihood of occurrence of unfavorable pleural developments.

Approximately the same proportions of patients with far advanced and moderately advanced lesions developed pleural effusions (table 6). However, the difference in the relative number of empyemata was striking. The pneumothoraces were complicated by empyema more than three times as frequently in the far advanced cases as in the moderately advanced cases. This direct relationship between the original extent of the tuberculosis and the subsequent appearance of purulent effusions has been noted by Bronfin (6), Cutler (16), Hayes (18) and others. In Myers' (25) series of 239 pneumothorax cases, empyema developed in 3 per cent of the minimal cases, in 5 per cent of the moderately advanced cases and in 15 per cent of the far advanced cases.

The frequency of empyema as a complication in pneumothorax therapy as recorded by most investigators is very similar to that in our series. Rosenthal (19) observed empyemata in 5 to 10 per cent of his pneumothorax cases, Eglee and Jones (12) in 8 per cent, Mayer and Dworkin (22) in 10 per cent, Burrell (15) in 12 per cent. Heaton (8) reviewed the literature and found empyemata present in 8 per cent of 2,485 pneumothorax cases. Other observers have encountered the complication in an even greater proportion of cases; Bronfin (6) in 18.7 per cent, Coryllos (20) in 15 to 20 per cent and Hayes (18) in 21 per cent.

Most of the empyemata in our patients had their origin in serous effusions of long standing. In only a few was the fluid purulent from the beginning and nearly all of those followed in the wake of a rupture of the corresponding lung. If we consider the initial occasion on which the

TABLE 6

Relation of original stage of disease to development of pleural effusions in course of pneumothorax therapy

	NUMBER OF PNEUMOTHORAX CASES	FLUID IN COSTOPHRENIC SINUS	FLUID ABOVE DIAPHRAGM	EMPYEMA
Moderately advanced...	60	52 (86.7%)	25 (41.7%)	2 (3.3%)
Far advanced.....	254	216 (85.0%)	102 (40.2%)	30 (11.8%)
Totals.....	314	268 (85.6%)	127 (40.3%)	32 (10.2%)

fluid was found to be purulent as the time of the onset of the empyema, the average duration of the pneumothorax when the empyema was first noted was eighteen months. In one case a purulent effusion made its appearance only four weeks after the institution of the pneumothorax. In only 6 other instances of a total of 32, however, did the empyema develop within the first year of treatment. On the whole, the development of empyema in our patients occurred definitely later in the course of their pneumothoraces than has been observed in younger patients.

Three of the empyemata in our series, comprising 1 per cent of the total of 314 pneumothorax cases, became secondarily infected with pyogenic organisms. In each instance the mixed infection was the consequence of the creation of a bronchopleural fistula by the spontaneous rupture of the collapsed lung. In none of the cases was the

collapse effective in closing the cavity, despite the addition of the superimposed spontaneous pneumothorax. All three of the patients died in a comparatively short time. The percentage of mixed-infection empyemata in our group was slightly smaller than that reported by other observers, such as the 1.5 per cent noted by Brock, Mullen and Woodson (21) and the 2 per cent recorded by Heaton (8) and by Eglee and Jones (12).

Rupture of the lung, either spontaneously or following the perforation of the visceral pleura by the point of the needle, was noted in 15 (4.8 per cent) of our 456 cases. The actual number of traumatic pneumothoraces attending the initial administration of air probably was much larger, with the majority of the accidents going unnoticed because the patients displayed no alarming symptoms. Virtually all of our patients who developed undue dyspnoea because of the sudden increase in the size of their pleural space were patients whose contralateral lung was extensively diseased; patients with a unilateral lesion and an adequate vital capacity usually experienced little or no respiratory distress. One patient died within twenty-four hours of the production of a traumatic pneumothorax during the attempted induction of an artificial pneumothorax. The three cases wherein spontaneous rupture of the lung led to the development of a mixed-infection empyema, with ultimate death of the patients, have already been mentioned. A spontaneous pneumothorax on the opposite side occurred in two of our cases; in neither instance was the subsequent course of the collapse therapy significantly affected.

In three of our cases the first attempt to introduce air gave rise to air embolism, presumably from the inadvertent introduction of air into a blood vessel. One of the three patients died soon after the occurrence of the accident. The other two recovered, one after a temporary attack of blindness, the other after a transient hemiplegia; there were no permanent sequelae.

An obliterative pleuritis which resulted in the eventual loss of the pneumothorax space occurred in 10 (10.9 per cent) of our successful cases. In every instance the collapse had been in effect more than a year at the time the pleural surfaces first began to exhibit adhesive tendencies. One pneumothorax was three years old when this complication developed. A long-standing effusion large enough to cover the diaphragm was present in every case. All of these patients were followed for some length of time after the enforced reëxpansion of their previously collapsed lungs, but no reopening of cavities was observed.

DISCUSSION

Weighing the results and the complications attendant upon its use in our series of cases, we find it logical to conclude that artificial pneumothorax is a procedure of distinct value in the treatment of the tuberculous patient over forty. True, it is not as effective in patients in the fifth decade as it is in younger persons. But, then, neither is any other measure in our therapeutic armamentarium. In our series, artificial pneumothorax was instrumental in achieving the arrest of the disease in approximately one patient in every five to whom it was applied. We must not forget that at the time of the institution of the collapse therapy the average duration of the tuberculosis in our patients was nearly four years and the lesion was far advanced in more than four-fifths of the cases. It is reasonable to assume that, had pneumothorax generally been induced earlier in the course of the disease, the results would have been much more gratifying.

The various complications of artificial pneumothorax occurred with no greater frequency among our patients than that with which it has been observed in younger persons. Death was due directly to the complications of pneumothorax in 5 patients: air embolism in 1, traumatic pneumothorax in 1 and mixed-infection empyema in 3. Sixteen of our patients who died had pure tuberculous empyemata; it is difficult to estimate the degree in which the presence of intrapleural pus contributed to these deaths, for in all 16 cases the pulmonary lesion was actively progressive. However, even if we should assume that the empyema was the cause of death in each of these 16 patients, the fatalities consequent to complications would number only 21, or approximately 4.9 per cent of the patients treated. Heaton (8), after making an exhaustive survey of the literature, is of the opinion that serious and fatal complications of artificial pneumothorax may be expected in 4 to 5 per cent of cases.

If artificial pneumothorax is to be induced in a person in the fifth decade of life, it should be done as early in the course of the disease as possible. The shorter the period of time the patient has been ill and the less extensive his lesion, the greater are the chances for the success of the therapy and the smaller the probability of occurrence of empyema. Closure of the cavity in successful cases is effected earlier in patients whose disease history prior to the institution of pneumothorax has been brief, the time interval bearing a direct relation to the length of the

previous history. It is true that pleural effusions are more likely to supervene in persons who have had tuberculosis only a short time. However, our primary aim in collapse therapy is the cure of the pulmonary disease, not the avoidance of a complication that is of little practical significance in the great majority of cases.

An obviously ineffective pneumothorax should be abandoned as soon as it becomes apparent that success is out of the question, regardless of the age of the patient. In cases where the ultimate result is in doubt, however, the age of the patient should seriously influence our decision concerning the continuance or discontinuance of the collapse. It has been shown rather conclusively that the time interval of cavity closure and sputum conversion varies directly with the patient's age; in our series most of the pneumothoraces became successful in the latter half of their first year, the average time being approximately nine months. It seems advisable, therefore, to maintain pneumothoraces of doubtful efficacy for a somewhat longer time in persons over forty than would be wise in younger patients. The objection to the futile prolongation of any useless pneumothorax is two-fold: (*1*) the postponement of the application of other collapse therapy measures which may be feasible, with consequent reduction in the likelihood of their success because of this delay and (*2*) the ever-increasing danger of complications, particularly empyema. In deciding upon the time of abandonment of a doubtful collapse, we must carefully weigh these two factors against the longer time of conversion in older patients, taking into consideration the fact that other methods of collapse are not as effective in older patients as they are in younger ones, as well as the fact that empyema tends to develop somewhat later in the course of pneumothorax therapy in older persons. We must not lose sight of the fact that empyema has its greatest incidence in unsuccessful pneumothoraces which have been maintained too long.

Bilateral pneumothorax appears to have a definite place in the treatment of tuberculous patients over forty. Properly administered in carefully selected cases, it is well tolerated and ordinarily occasions no marked respiratory embarrassment. In our small group of 25 patients, its success compared favorably with that of pneumothorax as employed unilaterally by us in a larger series of cases.

The surgical division of pleural adhesions is necessary to the completion of the collapse in a large number of persons in the fifth decade, just as it is in younger patients. More than 20 per cent of the successful

pneumothoraces in our series would have been ineffective, if we had failed to make use of this valuable therapeutic adjunct. Thoracoscopy is a simple procedure which subjects the patient to only a minimal amount of danger. Unless the nature of the collapse obtained is such that the outlook for success is hopeless from the beginning, direct inspection of the pleural cavity by the closed method should be given serious consideration in virtually every case before a pneumothorax made ineffective by pleural adhesions is discontinued and the lung permitted to reëxpand. The decision to proceed with the pneumonolysis after actual examination of the offending adhesions depends on a variety of factors: the character and structure of the adhesions, the possibility or impossibility of their being effectively severed, the ease with which they can be cut and the dangers incident to a difficult and prolonged dissection as compared with those attending the termination of the pneumothorax and the institution of an alternate collapse measure. In cases with unilateral disease, discontinuance of the pneumothorax in favor of a subsequent thoracoplasty is usually preferable to a hazardous pneumonolysis; whereas in bilateral disease, a pneumonolysis, even though it is technically difficult and beset with considerable danger, may be the patient's only hope. In any event, a thoracoscopic inspection should be made before we decide that nothing further can be done to enhance the success of the collapse. The roentgenographic and fluoroscopic appearances of pleural adhesions are highly deceptive at times. They should not be accepted as substitutes for the direct examination of the adhesions.

Like all other forms of collapse therapy, artificial pneumothorax, although it is employed only as a temporary measure, has as its express purpose the permanent cure of the pulmonary lesion. Its worth is to be appraised, therefore, not merely in the light of its success in effecting and maintaining closure of the cavities during the collapse of the diseased lung, but also in regard to its efficacy in assuring that the closure will be lasting. We regret that the scope of our survey is rather limited in this respect. Of the 92 successfully collapsed lungs in our series, only 21 had reëxpanded at the time this paper was written. In 9 instances the pneumothorax was discontinued because it was considered to have achieved the desired end. Two of the patients refused further refills, one after fourteen months of treatment, the other after twenty-two months. In the other 10 cases the reëxpansion followed the development of an obliterative pleuritis. Twelve of the 21 patients remained

under our observation for more than a year after the reëxpansion of their previously collapsed lungs. There was no indication of a recrudescence of the lesion in any of these 12 patients or in any of the others who were followed by us for a shorter period of time. Thus far it appears that artificial pneumothorax is enduring in its effect in persons over forty, but it is far too early for us to form any definite conclusion. Complete evaluation of the results in our series must await the time when most or all patients in the successful group have been observed for a sufficient length of time after reëxpansion to permit accurate estimation of the lasting effectiveness of their pneumothoraces.

SUMMARY AND CONCLUSIONS

1. A comprehensive study of the results and complications of pneumothorax therapy in 431 World War veterans over forty years of age is presented.

2. Artificial pneumothorax, successful in 20.2 per cent of the cases attempted, is a distinctly worthy therapeutic measure in patients in this age group. Bilateral pneumothorax is of definite value.

3. The incidence of complications in our series was no greater than that generally observed in younger patients.

4. If pneumothorax is to be induced, it should be started as early in the course of the disease as is possible.

5. Because the average time interval of cavity closure and sputum conversion is longer, it may be necessary to continue a pneumothorax of doubtful efficacy slightly longer in persons in the fifth decade than would be advisable in younger patients. It should not be maintained indefinitely, however.

6. The surgical division of pleural adhesions is necessary to the successful completion of the collapse in a large number of patients.

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TUBERCULOSIS CASE-FINDING

An X-Ray Survey of 28,331 Trade Union Members in New York City, 1939

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The New York City Department of Health has been interested in accumulating data on the prevalence of chronic pulmonary tuberculosis among apparently healthy adults since 1933 (1). A considerable proportion of this work has been directed to the unemployed and relief populations of the city until 1939 when an effort was made to survey certain groups of the population represented in some of the trade unions. The first survey among trade unions was conducted among members of the Furriers Joint Council (2). This report deals with other surveys among trade unions following the above survey, and represents the coöperation of an average of 25 per cent of the membership of eight different unions, the majority of which was among those working in the garment trades.

Certain occupations are known to be related directly or indirectly to various diseases, although it is exceedingly difficult, as Sydenstricker (3) has pointed out, to isolate the influence of occupation from the influence of all the other environmental factors. However, it is of interest to see what facts the examination of industrial groups may reveal, even though no causal relationship can be assigned.

The results of the data presented herewith, composed largely of the findings among members of the International Ladies Garment Workers' Union, are particularly interesting in view of the fact that a previous survey of this group in 1914 by the United States Public Health Service (4) showed a rate of 6 per 100 white males with chronic pulmonary tuberculosis, on the basis of a physical examination.

It must be appreciated that the above study is not readily comparable to the material to be reported herewith because routine physical examination will not detect the early infiltrations with the accuracy of the roentgenogram; also, the conditions under which these workers operate to-day is vastly different from those in 1914.

[1] Bureau of Tuberculosis, New York City, Department of Health.
[2] Milbank Memorial Fund.
[3] Milbank Memorial Fund.
[4] Bureau of Tuberculosis, New York City, Department of Health.

In the present studies the Department of Health of New York City made available free chest roentgenograms and the necessary follow-up studies to diagnose accurately the members of certain locals. The union coöperated by issuing publicity, and through personal contact urged its members to take advantage of the service, but there was no compulsion. Undoubtedly there were some selective factors operating in a survey of this type, and it is impossible to say whether or not they are factors which would influence the amount of illness found. The degree of coöperation varied widely in the different unions and, in general, represents differences in the method of organization used by the union leaders (table 1). It was found that better results were obtained when the membership was occupied, rather than during periods

TABLE 1

Incidence of clinically significant tuberculosis found in 28,331 members of trade unions, New York City, 1939

ORGANIZATION	TOTAL UNION MEMBERSHIP	NUMBER X-RAYED			PERCENTAGE OF UNION MEMBERSHIP X-RAYED	CLINICALLY SIGNIFICANT TUBERCULOSIS	
		Total	Male	Female		Number	Per cent
Needle trades	94,293	24,013	6,196	17,816	25.5	150	0.6
Dressmakers	72,087	9,379*	4,707	4,671	13.0	64	0.7
Negligee	9,956	6,428	88	6,340	64.6	47	0.7
Knitgoods	3,750	2,546	991	1,555	67.9	17	0.7
Bathrobe and children's wear	8,500	5,660	410	5,250	66.6	22	0.4
Department store	1,440	680	276	404	47.2	10	1.5
Wholesale warehouse	4,500	544	410	134	12.1	0	—
Pocketbook workers	3,200	1,966	1,338	628	61.4	8	0.4
Food trades	8,000	1,128	1,120	8	14.1	11	1.0
Total	111,433	28,331	9,340	18,990	25.4	179	0.6

* Includes one individual with race and sex not specified.

of unemployment. It was possible to schedule the examinations so that no time would be lost from work and yet the maximum number could be X-rayed per day.

There are four branches of the Needle Trade Unions represented in this study, comprising 24,013 members, or 25 per cent, of the total membership reported at the time of the survey. The individual summary of the findings in each are detailed below.

NEEDLE TRADE WORKERS

Dressmakers: The sample of dressmakers X-rayed included 9,379 who were drawn chiefly from Locals 10, 22, 60 and 69; the balance was drawn from the

Cloakmakers and Auxiliary Trades. The sample was heavily weighted with members of Local 22, since this local constitutes only 37 per cent of the total dressmakers, compared with 67 per cent of the total sample. Local 60 had approximately the same representation in the sample as in the total groups. The proportion of workers X-rayed who belonged to Local 10 and to Local 89 was lower than the proportion that each of these locals formed of the total dressmakers. Thus, it should be kept in mind that any characteristics or peculiarities of Local 22 will have undue weight in the results for the total sample, whereas any special characteristics of Local 10 or Local 89 will be minimized.

Of the 9,379 X-rayed, 4,707, or 50.2 per cent, were males and 4,671, or 49.8 per cent, were females. Of the total 9,149, or 97.5 per cent, were white and the remainder colored, a group too small to have significance. Fifty-two per cent of the entire group were forty years of age or older.

Five hundred and seven, or 5.4 per cent, of the total X-rayed were classified as chronic pulmonary tuberculosis. Five hundred of these cases occurred among the white. Sixty-four, or 0.7 per cent, of the total were classified as clinically significant; all were among the white group and represented 12.6 per cent of all the chronic pulmonary tuberculosis found.

Of those considered clincially significant 32, or 50 per cent, were minimal in extent, 26, or 40.6 per cent, were moderately advanced and 6, or 9.4 per cent, were in the far advanced stage.

Negligee workers: The Underwear and Negligee Worker's Union was chosen because the age and sex of its members seemed to offer special advantages for case-finding. The members were predominantly young females in the age groups where tuberculosis mortality rates are highest. Sixty per cent were under thirty years of age.

A total of 6,428 was X-rayed; 6,340, or 98.6 per cent, were females and 88, or 1.4 per cent, were males. There were 6,008 white persons, or 93.5 per cent.

One hundred and eighty-four, or 2.9 per cent, of the total were classified as chronic pulmonary tuberculosis. Of this number, 175 were white and 9 colored; 47, or 0.7 per cent, of the total showed lesions of clinical significance, which represented 25.5 per cent of all the chronic tuberculosis found.

Of those considered clinically significant 30, or 63.8 per cent, were minimal, 11, or 23.4 per cent, moderately advanced and 6, or 12.8 per cent, in the far advanced stage.

Knitgoods: A total of 2,546 was X-rayed of which 1,555, or 61.1 per cent, were female and 991, or 38.9 per cent, male; 2,508, or 98.5 per cent, were white; 47 per cent were under thirty years of age.

Ninety individuals were classified as chronic pulmonary tuberculosis, all being in the white population and giving the group a percentage of 3.5. Seventeen individuals, or 0.7 per cent of the total examined, were classified as clinically significant.

A classification according to stage of disease showed 9 to be minimal, 7, moderately advanced and one far advanced.

Bathrobe and children's wear: Interest in this group was based largely on the fact that the membership was made up of young females of Italian extraction.

A total of 5,660 was X-rayed; 5,250, or 92.8 per cent, were females. There were 4,990, or 88.2 per cent, white. Sixty-one per cent were under thirty years of age.

One hundred and thirty-one, or 2.3 per cent of the total, were classified as chronic pulmonary tuberculosis, 111 being white, 13 Negro and 7 not classified. Twenty-two, or 0.4 per cent of the total, were considered as clinically significant. This was 16.8 per cent of all tuberculous lesions found.

Classification according to stage of the disease showed that of those considered significant, 10 were minimal, 9 moderately advanced and 3 advanced lesions.

In order to compare the amount of significant tuberculosis among the four types of needleworkers, the total rates for each sex were adjusted for age. This adjustment was made up applying the rate for each age group to the age distribution of the total male and female workers X-rayed. The adjusted rate for male dressmakers and for male knitgoods workers was the same, 0.9 per 100. The number of male children's wear workers X-rayed was not large enough to make a comparison with that group reliable. Among the white females, the dressmakers and negligee workers each had an adjusted rate of 0.7 per 100 and the knitgoods workers had a rate of 0.6 per 100 persons X-rayed. The lowest rate among females was noted for the children's wear workers where the adjusted rate was 0.3 per 100. The rates are strikingly similar for dressmakers, negligee workers and knitgoods workers. Although the rate for white, female, children's wear workers is lower than the rate for any other female group of garment workers, the difference between this

rate of 0.3 and the highest rate 0.7, noted for white, female dressmakers and negligee workers, is not large enough to be considered significant.

The general nativity of the members of the foregoing unions was analyzed and in general there was a preponderance of foreign born. This ranged from 83 per cent among the white dressmakers to 36.2 per cent among the bathrobe and children's wear workers. The native born of foreign parentage composed almost all of the rest of the workers in all four unions, less than 10 per cent being native born of native parentage in any group.

The remaining four union groups included in this study, while similar in some respects, had an entirely different type of occupation and will therefore be summarized individually. The percentage of persons who coöperated is shown in table 1.

DEPARTMENT STORE EMPLOYEES

This survey represents a fair cross-section of a large and active department store in New York City. It was organized through the union, and through their arrangement the X-ray unit was set up in the store, thus greatly facilitating the job and causing no appreciable loss of time from duty by the employee. The employers extended to the union every facility for coöperation.

Of the 680 employees X-rayed, 404, or 59.4 per cent, were female and 276, or 40.6 per cent, were male. There were only 4 Negroes in the group, and they showed no lesions. Sixty-five per cent were under thirty years of age.

Chronic pulmonary tuberculosis was found in 25, or 3.7 per cent of the total; 10, or 1.5 per cent of the total, were classified as clinically significant which represents 40 per cent of the total tuberculosis found. The classification of disease by stage was 7 minimal and 3 moderately advanced.

WAREHOUSE WORKERS

The survey among the warehouse workers represents the lowest percentage of persons X-rayed from the total membership for any of the unions studied thus far, due in large part to inability to set up a survey centre immediately accessible to the workers in this trade.

Of the 544 members X-rayed, 410, or 75.4 per cent, were male, and 134, or 24.6 per cent, were female. White persons represented 98.5 per cent of the total; 80 per cent were under thirty years of age.

There were 10, or 1.8 per cent of the total, all white, who were classified as chronic pulmonary tuberculosis; all were considered as arrested.

POCKETBOOK WORKERS

Of the Pocketbook Workers Union, 1,966 members were X-rayed; 1,338, or 68.1 per cent, were male and 31.9 per cent female. White persons predominated, forming 99.5 per cent of the total; 62 per cent were under forty years of age.

Chronic pulmonary tuberculosis was diagnosed in 105, or 5.4 per cent of the total; 83 cases were males and 23 were females; 8, or 0.4 per cent, of the total X-rayed were classified as clinically significant. These cases were evenly divided between males and females. The classification by stage of the disease showed 2 minimal and 6 moderately advanced.

FOOD-TRADE WORKERS

This union represented a group of the population among whom we were anxious to secure as high a degree of coöperation as possible, because a previous survey by Martin *et al.* (5) had indicated an incidence of 2 per cent with significant lesions. Furthermore, there are estimated to be 300,000 persons in New York City engaged in various phases of food-handling trades. If the prevalence of disease quoted above could be considered as a fair cross-section, then examination of the total might be expected to reveal approximately 6,000 cases of significant tuberculosis.

The union leaders of the group included in this study were obviously interested in the importance and value of the survey, because it would permit them to recommend their membership to the trade as being free of tuberculosis. However, it appeared that their attitude was not shared by their members. The lack of coöperation seemed to stem from the fact that the members were hazy in their own minds as to its value, and of course there was the fear of a possible loss of the job. Thus, the low percentage of persons coöperating represents a lack of education and organization of the membership on the part of the union officials, because when these efforts were known to be more methodical in other unions the coöperation has always been greater.

Of the 1,128 members X-rayed, 1,120, or 99.3 per cent, were male and 8, or 0.7 per cent, female; 94 per cent were white, and 53 per cent were under forty years of age.

There were 53 cases of chronic pulmonary tuberculosis, or 4.7 per cent of the total; 11, or 1.0 per cent, of the total X-rayed were considered as

clinically significant. All were white males and represented 20.8 per cent of all the chronic pulmonary tuberculosis found.

The classification of the 11 cases by stage of the disease showed 5 minimal, 5 moderately advanced and 1 far advanced.

DISCUSSION

The incidence of clinically significant tuberculosis is shown for groups of unions in table 1. The absence of important tuberculosis in warehouse workers is not significant because of the small number X-rayed. It is obvious that workers in department stores and food-handlers had higher rates of significant tuberculosis than workers in the needletrades and the pocketbook workers. Other more detailed analysis by specific union locals showed a greater problem in some, but in no instance has it been possible to conclude that the job *per se* represented a special hazard so far as tuberculosis is concerned. There has long been an opinion that the food trades, for example, attract a less physically fit type of employee than other trades, but in the studies thus far, there has been no evidence to justify this opinion.

The distribution of the 28,031 persons included in this study by age, sex and color is consolidated for convenience in table 2. The population is predominantly white, with females forming two-thirds of the total. Negroes constituted only a small percentage (4.5) of the total and the numbers are too small for detailed analysis. However, the incidence of disease among the Negroes in these studies is not dissimilar to the findings in other mass surveys when persons above twenty-five years of age are considered.

The distribution of chronic pulmonary tuberculosis and clinically significant lesions found in the entire group are summarized in table 3. It is obvious that a higher percentage of both types of lesions was found in white males than in white females. The incidence of lesions among the colored was lower than in the white, and no lesions were found among the Negroes under twenty-five years of age, although a fair percentage of their total population was under that age. Previous mass surveys (1) have usually shown more significant disease among the colored below twenty-five years of age than has been found at the same ages in the white group.

In the organization of these surveys there has been a definite division of responsibility between the union and the Department of Health. The union has accepted the responsibility of education and organization

of their membership for the survey. This has been done in various ways. Basic information on the importance of tuberculosis and its estimated prevalence in varying types of population was made available to the union by the Department. They then used the material in the way best suited to their membership. In most instances the union first attempted to sell the idea to its official group, including the leaders in the

TABLE 2

Incidence of chronic and clinically significant pulmonary tuberculosis found in 28,331 members of trade unions X-rayed in New York City

AGE GROUP	PULMONARY TUBERCULOSIS											
	Chronic						Active*					
	White		Negro		Unknown		White		Negro		Unknown	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
5– 9.9												
10–14.9												
15–19.9		5						4				
20–24.9	6	70				2	5	38				
25–29.9	22	80		2		1	7	25		2		
30–34.9	35	74		7		2	13	10		3		
35–39.9	47	82	1	4	2		7	6		1		
40–44.9	100	73	3	3		1	11	9				
45–49.9	104	53		3	1		8	6		1		
50–54.9	130	30	1	3			12	1				
55–59.9	82	11					7					
60–64.9	32	10					2	1				
65–69.9	14	3				1						
70–74.9	1											
75–79.9	1											
80–84.9												
85–89.9												
Unknown												
Totals.....	574	491	5	22	3	7	72	100		7		

* Clinically significant.

various shops. In many instances the proposition was placed before general meetings of the union; occasionally educational films were shown and in some instances representatives from the Department addressed these groups. One union at its own expense reprinted one of the Department's leaflets on tuberculosis for distribution to its membership. The various trade journals of the unions also carried fairly extensive

news items prior to and during the survey. This information reached not only the local members but union workers throughout the country, and was responsible for the creation of interest in other union organizations, both here and elsewhere. The Department of Health also provided posters for display at union headquarters which tended to keep the idea before the hundreds who, for various reasons, regularly visit these places.

TABLE 3

Age, race and sex distribution of 28,331 members of trade unions, X-rayed in New York City

AGE GROUP	NUMBER X-RAYED	SEX		RACE			SEX AND RACE					
							White		Negro		Unknown	
		Male	Female	White	Negro	Unknown	Male	Female	Male	Female	Male	Female
10–14.9	1		1	1				1				
15–19.9	1,296	129	1,167	1,279	10	7	127	1,152	2	8		7
20–24.9	5,403	743	4,660	5,252	123	28	727	4,525	16	107		28
25–29.9	5,455	1,070	4,385	5,091	326	38	1,041	4,050	27	299	2	36
30–34.9	3,698	1,072	2,626	3,365	295	38	1,046	2,319	19	276	7	31
35–39.9	3,757	1,279	2,478	3,462	270	25	1,249	2,213	21	249	9	16
40–44.9	3,343	1,487	1,856	3,195	128	20	1,468	1,727	10	118	9	11
45–49.9	2,582	1,480	1,102	2,498	69	15	1,468	1,030	4	65	8	7
50–54.9	1,650	1,146	504	1,609	35	6	1,139	470	3	32	4	2
55–59.9	750	614	136	737	7	6	607	130	1	6	6	
60–64.9	291	239	52	286	4	1	238	48		4	1	
65–69.9	87	66	21	85	2		66	19		2		
70–74.9	11	11		11			11					
75–79.9	2	2		2			2					
80–84.9												
85–89.9	1		1	1				1				
Unknown	4	2	2	3	1		2	1		1		
Total.....	28,331	9,340	18,991	26,877	1,270	184	9,191	17,686	103	1,167	46	138

The Department of Health in coöperation with its WPA Project provided without cost the entire survey and, through Department sources, the necessary follow-up for significant cases. The contribution by WPA consisted chiefly of clerical and statistical services; the cost of the X-ray pictures was financed by funds provided for WPA by the City of New York for all materials and supplies of all WPA Projects operated in New York City.

The program was set up on the basis that all diagnostic findings would be held in strict confidence between the Department of Health and the

individual X-rayed. The diagnosis in any case would not be released to private physicians, union medical services or others without the consent of the individual manifested by a signed waiver.

As in all our surveys final diagnoses were not made on the survey X-ray picture alone, but following a second examination including history, physical examination, sputum tests, repeated roentgenograms or such other data as were pertinent. All cases were registered in our Branch Offices and the same method of contact follow-up instituted as in any regularly reported case. Thus, the survey was not a device to merely find a case, but rather to locate and place under supervision the case and his contacts for a time sufficient to control the disease. The majority of all cases found in these surveys has become the routine responsibility of the Department of Health. The Union Health Centre, representing the majority of workers in the needle trades, assumed the major part of the subsequent supervision of cases after a final classification had been made by the Department of Health.

It was part of the agreement between the Department of Health and the union, that if the survey indicated a tuberculosis problem, the union would make plans for another survey in the future, the expense to be borne as far as possible by the union. Thus far, none of the unions reported here have organized a definite survey, although some have asked for the continued assistance of the Department. The available funds in the unions have not been adequate in most instances to undertake the full responsibility, nor do they possess the technical staff requisite to such a service. Thus, the Department of Health may extend its services to unions presenting a problem and whose membership has shown a high degree of coöperation in the past. It is the purpose of the survey to indicate a problem and the method of its control, with the idea that the union will eventually make it a part of its health program.

Several of the unions[5] have made notable contributions to the present program by providing the cost of hospital care for their members in noncity institutions or by the payment of benefits in a lump sum. As nearly as can be estimated these contributions during the first six months following the survey have totalled over $10,000.00 and they have been of

[5] A detailed account of the contributions made on behalf of those union members entitled to assistance through the International Ladies Garment Workers' Union will be found in the report of the Union Health Center, 1913–1940, I.L.G.W.U., 275 Seventh Avenue, New York City, by Dr. George M. Price, Director.

the greatest importance in consideration of the limited bed facilities available in the City. Some patients have returned to their jobs as arrested. Some unions have suggested that the coöperation of their membership might be greater if the individual were required to pay a fee. This is of course in line with the Department plan of placing as large a part of the cost as possible on the union.

The experience in conducting these surveys has clearly indicated several important facts affecting the success of the program. Primarily the worker is fearful that if tuberculosis is discovered he will lose his job. This, of course, is inevitable if the lesion is active. In such cases some unions recall the union card, and the member is therefore out of work unless he can secure a job in a nonunion shop. Those unions which have sickness and hospital benefits are in a better position to convince their members that if disease is found adequate care will be provided for the case and his family, than those which do not have such facilities. Several unions in these studies did not have such backing and, therefore, the individual had to rely upon City aid in the event that he had to stop work.

The intensity of the publicity and the general educational plan of organizing a union for the survey seemed to bear a direct relation to the degree of coöperation of the membership. However, where these efforts were well developed there was also more definite activity on the part of the union leader and his staff down to the individual shop leaders. It appears that this latter activity is of the greatest importance in securing coöperation from the individual members. As most shops are small, it is possible for the shop leader to contact each member individually and clear up any indecision on his part.

It was also found that a better response was obtained when the survey was conducted in the union headquarters rather than in another building not frequented by the union member.

Considering the problem as a whole, the findings in our studies of a few unions indicate that a real problem of tuberculosis exists and it is of sufficient magnitude to require a permanent program of case-finding. These surveys in most instances will reveal the majority of cases in a minimal stage, or if the first survey shows a low percentage of minimal lesions, a subsequent study would undoubtedly increase the number found. Each new member should be X-rayed and an annual survey of all members would undoutedly be a potent means of eradicating the

disease in a large part of the industrial population. Early detection results in early and more permanent cure for the individual and, in turn, will effect vast savings for the union and society at large.

In the development of this type of program it would be to the advantage of the employer to coöperate with the union in defraying the cost. One hindrance at this time in such a plan is the fact that labor feels that in case of illness it might be discriminated against unjustly. It should be possible for the two to enter an agreement that would be fair and mutually beneficial. Undoubtedly, many expert technicians could be conserved for industry who, if neglected, would not only be lost to industry, but eventually would become a greater burden to society because of illness or death.

CONCLUSION

The surveys among 28,331 union members may be summarized as follows:

Twenty-eight thousand three hundred and thirty-one, or over 25 per cent, of the total members on the rolls of the various unions that coöperated with the Department of Health in this survey responded to the opportunity to participate.

The average age of the entire population was 32.2 years; 26,877, or 94.9 per cent, were white; 1,270, or 4.5 per cent, were Negroes; and 184, or 0.6 per cent, were of unknown races.

In the white population 9,191, or 34.2 per cent, were male, and 17,686, or 65.8 per cent, were female. In the Negro population 103, or 8.1 per cent, were male, and 1,167, or 91.9 per cent, were female. In the unknown race group 46, or 25 per cent, were male and 138, or 75 per cent, were female.

One thousand one hundred and two cases, representing 3.9 per cent of the total population X-rayed, were diagnosed as having chronic pulmonary tuberculosis; 1,065 (574 male, 491 female), or 96.6 per cent of the cases, were found among the white group; 27 (5 male, 22 female), or 2.5 per cent, among the Negroes and 10 (3 male, 7 female), or 0.9 per cent, among the unknown group.

One hundred and seventy-nine, or 16.2 per cent, of the persons with chronic tuberculosis were classified as clinically significant. This represented 0.6 per cent of the entire population; 172, or 96.1 per cent, were white (72 male, 100 female) and 7, or 3.9 per cent, were Negroes (all female).

Of these clinically significant cases, 95, or 53.1 per cent, were in the minimal stage; 67, or 37.4 per cent, were moderately advanced and 17, or 9.5 per cent, were far advanced.

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DIAMETERS OF NORMAL AND ABNORMAL BRONCHI[1]

A Statistical Study

JOHN CHAPMAN AND HOWARD E. SMITH[2]

Although much literature has appeared on the subject of bronchiectasis, when we looked for a statement as to the normal size of the bronchi which participate most frequently in dilatations, we were unable to find it. The only periodical reference to measurements made from the bronchogram is very recent (11) and was not undertaken for the purpose of determining diameters. Nor are the bronchi measured by this writer, except occasionally those involved in dilatation. The standard textbooks of anatomy to which we have had access offered no information (2, 9), nor have applied and surgical anatomy texts contributed knowledge (4, 5). In his monograph the only measurements with which Miller (7) deals are those on fine, terminal branches, for the most part of no significance in bronchiectasis. Jackson in an extensive discussion of bronchoscopy gives no bronchial measurements (6), nor do Norris and Landis (8), or Graham, Ballon and Singer (5).

Even should figures drawn from necropsy or cadaver material be available, it is certain that our measurements from clinical material will more nearly represent the normal, living bronchus and will consequently be of more value in the study of bronchograms. So that, even though our method is indirect in comparison with the direct methods of the dissecting table, and certainly, therefore, less exact, it may represent an accurate approximation of conditions during life.

The material of this study consists of bronchograms on about 200 patients. They were all made at the standard distance of six feet and all in the posteroanterior diameter, except a few homolateral oblique ones in which little distortion was produced since the injected side was against the cassette. Naturally all bronchograms were made at the end of deep inspiration. Since the standard teleoroentgenogram gives practically true measurements, it is a fair assumption that our figures for bronchial diameters approach the actual fairly closely. All measurements are from lower lobe branches.

[1] From the State Sanatorium, Sanatorium, Texas.
[2] Austin, Texas.

The method of measurement was rather crude, but about as sensitive as the material permits. With the plate in the viewbox, a needle-point divider with a set screw was adjusted until the points fell upon the outer borders of the iodized-oil shadow, care being taken to keep the measurement at right angles to the axis of the bronchus. Readings were then taken from a steel rule graduated to 0.5 mm. We find this rather coarse limit to be satisfactory, because the shadows of the oil are far from perfectly defined, though our plates were made at 350 ma. and in one-tenth to three-twentieths of a second. A certain amount of fuzziness of the margin was always present, while it also appeared that the shadows are composed of very small dots. Readings of less than 0.5 mm. proved to be unreliable on account of this lack of perfect definition.

The choice of bronchi to be measured offered other difficulties. No system of nomenclature with which we are familiar identifies any bronchi beyond the largest rami of the primary bronchus. Bronchograms also produce a degree of superimposition at times that makes difficult identification even of large branches. Since our purpose, primarily, was to compare normal and abnormal branches, we decided to choose levels corresponding to the sites of dilatation in bronchiectasis. Accordingly we picked a bronchus, which we call "A," that is a characteristic branch of a basilaris ramus. This level is just below the orifice of the branch and usually falls about 1 to 1.5 cm. from the termination of the lower bronchus. The second bronchus, "B," is a typical branch in the mid-lung field, but care was taken to avoid the so-called primary bronchus (2) which appears as continuation of the lower lobe bronchus and runs toward the costophrenic angle, since this branch is larger than others at the same level. These are the bronchi most frequently involved in cylindrical bronchiectasis. The third bronchial level, really a bronchiole called "C," is the continuation of "B" and is distinguishable by the fact that it is usually the last dichotomous branch given off, while its branches appear to be thin and hair-like filaments leading very shortly to the alveoli themselves. A typical anterior branch of this level is about 1.5 cm. above the diaphragmatic shadow (figures 1 and 2).

THE SIZE OF NORMAL BRONCHI

We give below the means of our measurements, divided according to sex and side, in 110 cases showing no bronchial dilatation. The unequal numbers are due to the fact that in some cases we injected but a single side, that we injected a few more women than men and that bronchus "B" is much easier to measure than either of the other two levels con-

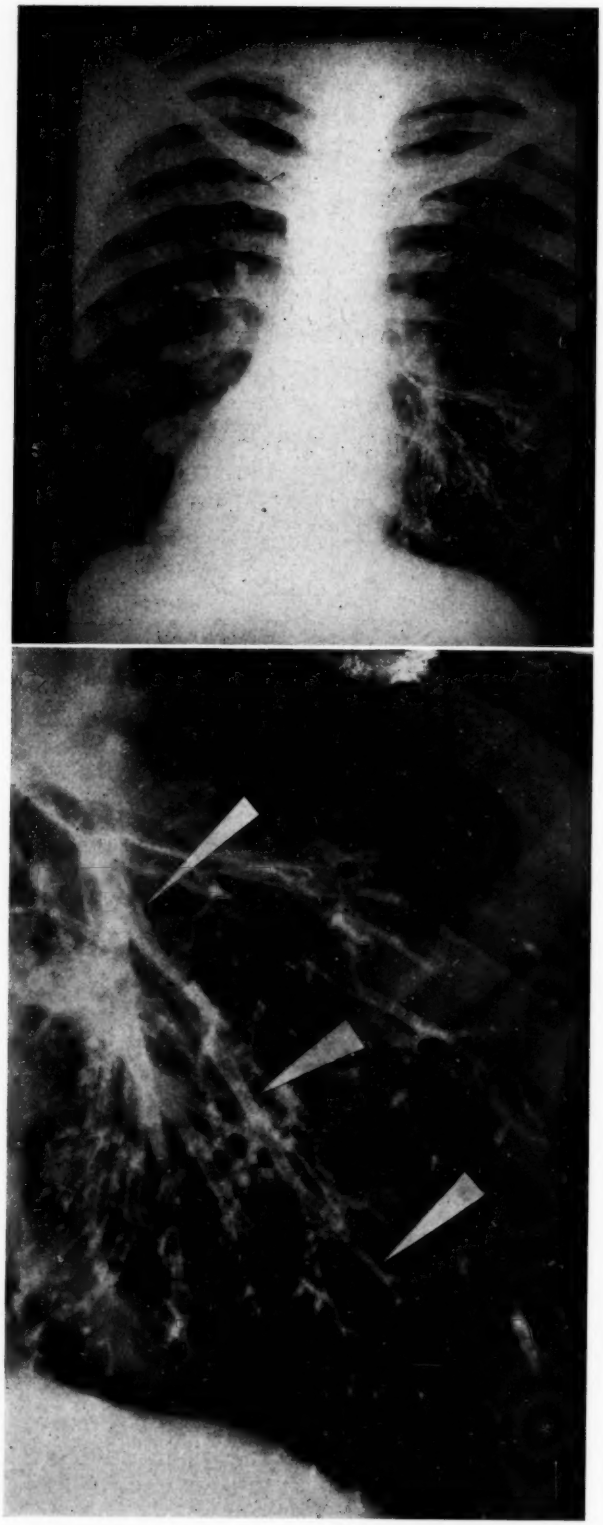

FIG. 1. Upper. Injection of a normal bronchial tree

FIG. 2. Lower. Enlargement from plate, indicating the levels at which bronchial diameters were determined.

sidered. "A" bronchus is sometimes obscured by over-lapping, while "C" may be overshadowed by alveolar filling or occasionally fails to fill on account of proximal blocking by mucus or secretions.

From table 1 it can be seen that diameters for corresponding levels are larger in men than in women, both on right and on left. On the other hand it will also be found that both in men and in women the branches of the left side are slightly larger than those on the right. These differences, however, are not significant. (The statistical methods used throughout are those given by Snedecor (10).)

TABLE 1

	RIGHT			LEFT		
	Number	Mean	Standard Error	Number	Mean	Standard Error
Men						
		mm.			mm.	
Bronchus A	52	4.85	.069	36	4.94	.098
Bronchus B	53	3.39	.058	38	3.54	.062
Bronchus C	50	2.14	.043	40	2.235	.0505
Women						
Bronchus A	50	4.76	.069	50	4.84	.0439
Bronchus B	57	3.25	.052	52	3.404	.0514
Bronchus C	55	2.01	.04	49	2.15	.044

COMPARISON OF NORMAL AND ABNORMAL BRONCHI

Comparison of normal with abnormal branches seemed to be the logical procedure to follow establishment of figures for normal diameters. In this study we chose to pair branches of the same individual, since frequently we find a normal contralateral side in cases of bronchiectasis and not rarely find normal branches even on the diseased side. Using this method we found that of 54 pairs of normal and abnormal bronchi "B," the mean difference was 2.12 mm., with a standard deviation of 1.1924 and a standard error of 0.1637. In the case of bronchus "C," 56 paired branches showed a mean difference of 2.31 mm., with a standard deviation of 1.321 and a standard error of 0.1765. Both of these differences with standard errors of the magnitude found are highly significant.

In the case of bronchus "A," unfortunately, we were not able to pair branches, since it was often impossible to determine which led to a series of dilatations and which did not. Overlapping at this level prevents the

use of bronchi on the same side. We therefore felt that we should have a much safer study if we compared normal and abnormal *groups* rather than paired branches from the same individual. Limiting the study to women, since biological characteristics would be similar in the two sexes, we compared 35 abnormal right branches with 50 normal right branches at the "A" level. The mean diameter of the normals was 4.76 mm., the mean of the abnormal branches 5.33 mm. The difference, 0.57 mm., was found to have a standard error of 0.1129 and is therefore highly significant. On the left side the mean normal diameter was 4.84 mm. and the mean abnormal 5.61 mm. The difference, 0.77 mm., was found to have a standard error of 0.1443 and is consequently also highly significant.

RELATIONS BETWEEN THE NORMAL BRONCHI OF THREE SIZES

In the beginning of our work we had hoped to be able to undertake a study of bronchial in comparison with tracheal diameters, assuming there should be an intimate relation in accordance with the principle of physiological gradience. Unfortunately, the trachea was so rarely properly outlined that accurate measurement was impossible and the idea had to be abandoned. Lacking this information we therefore decided to compare the diameters, using their logarithms for ease in handling, of the bronchi of the three levels mentioned above.

In this study we dealt only with measurements from women, since they furnished a larger series than the men, but we made no effort to distinguish between sides since it was shown above that the differences between them were not significant.

The regression of log A on log B produced in 45 cases a regression coefficient of 0.3537 with a standard error of 0.103. This regression coefficient and the correlation coefficient, which was found to be 0.4654, are both highly significant.

The regression of log B on log C in the same series of cases gave a regression coefficient of 0.6533 which, with a standard error of 0.17, is highly significant. For the same group the correlation coefficient was found to be 0.425, likewise a highly significant figure.

RELATIONS BETWEEN ABNORMAL BRONCHI AT THREE LEVELS

Having found that normal bronchi followed the principle of physiological gradience, it seemed logical to make the same test in regard to abnormal bronchi. In this study we used measurements on 35 women,

disregarding the side. The regression of log abnormal A on log abnormal B gave a coefficient of 0.5963 which with a standard error of 1.0764 is not significant; nor is the correlation coefficient of 0.322.

The regression of log abnormal B on log abnormal C gave a negative coefficient which was not further studied since it indicated that in bronchiectasis the normal relationship is reversed.

The findings in our study of bronchiectatic patients are certainly not unexpected. As a rule, though, there is a certain amount of dilatation in the A branches, as indicated by the figures showing their significant difference from the normal, it is the branches of B and C size which undergo considerable dilatation. So that, although it may in general be stated that the larger the dilatation at other levels, the larger will A branches be, there are enough variations from the statement that it may be a matter of chance. In the case of the regression of B on C, a negative correlation is precisely what might be anticipated in a series which included cases of saccular bronchiectasis.

RELATIONS BETWEEN BODY WEIGHT AND BRONCHIAL DIAMETER

At the time at which most of our bronchograms were made we had no spirometer and were unable to determine vital capacity. That relationship is one which should be studied and which we hope to present in another paper. Lacking such information for the present series, we made a study of relation of normal bronchial diameter to body weight, a datum closely related to vital capacity. On the other hand, body weight is a very variable factor, while bronchial diameter should theoretically be constant in healthy individuals.

In this study we used only a group of 32 women seen during the year preceding this work, since their weights had been recorded at the time the bronchograms were made and were relatively accessible. In these cases the regression coefficient log diameter bronchus A on log body weight was found to be 0.082, which, with a standard error of 0.13, is not significant. In the same cases the regression coefficient of log bronchus B on log body weight was 0.0498 which, with a standard error of 0.109, is insignificant.

RELATIONS BETWEEN BRONCHIAL DIAMETER AND TRANSVERSE THORACIC DIAMETER

Having found no significant relation between bronchial diameter and body weight, we thought of comparing bronchial diameter with the

greatest transverse thoracic diameter as determined from measuring the distance between rib shadows in our bronchograms. Had we had any record of anteroposterior thoracic diameter we should also have studied the relationship between that measurement and bronchial diameter. Such figures unfortunately were not available, but we hope at a later date to make such a study.

Using 45 women and measurements of bronchus B from the right side only, we found a correlation coefficient of 0.0309 which is insignificant. The regression coefficient of 0.0521 with a standard error of 0.1960 is also not significant.

We are unable to explain this apparent violation of a logical supposition—that the larger the diameter of the chest, the larger the bronchi. Possibly as the chest increases in size there is an increase in number rather than in size of bronchi.

COMMENT

It has been seen that in certain of our studies we have used branches from only one side or from one sex. In comparing transverse thoracic diameter with bronchus B, we carried the study no further, since it had already been seen that there is a highly significant correlation between the sizes of A, B and C.

The same is true of some of the other studies. Since we deal with biological data, there should be no difference in the relationships in the two sexes, and this point is further established by the fact that we were unable to show significant differences in the sizes of normal bronchi as to sides and as to sex.

CONCLUSIONS

1. The mean diameters and their standard errors according to side and sex are presented from a series of normal bronchograms, the levels of measurements having been determined by the importance of these levels in relation to bronchiectasis. No significant difference could be found between sides or between sexes at the same levels.

2. Comparison of normal with bronchiectatic bronchi showed highly significant differences of bronchial diameters at the three levels.

3. Study of the relation between body weight and bronchial diameter gave a positive regression coefficient, indicating a certain increase in bronchial diameter with increase in body weight, but statistically the relationship is not close enough to be regarded as significant.

4. A study of the relation between greatest transverse thoracic diameter and bronchial diameter showed a positive correlation and regression coefficient, but again the relationship was not sufficiently clear to be regarded as significant.

5. A study of the relationship between bronchi at each of the three levels resulted in highly significant correlation and regression coefficients, thus extending the principle of physiological gradience to the bronchial tree.

6. The relations of abnormal bronchi were such that, at the upper two levels, though there was a positive relationship, it was too slight to be significant. At the two lower levels, on the other hand, the relationship was inverted. These findings are explicable by the character and location of dilatations in bronchiectasis.

7. It is recognized that the study would have been more complete had study of the relation between bronchial diameter and anteroposterior diameter and vital capacity been possible. The relation between bronchial and tracheal diameters also requires study and we hope to present the results of such examination at a later time.

We wish to acknoledge our great indebtedness to the late Professor W. T. Dawson of the University of Texas School of Medicine for his encouragement and assistance in the preparation of the statistical part of this paper.

We wish to express our thanks to Dr. J. B. McKnight, Superintendent for permission to use records and plates in the files of the State Tuberculosis Sanatorium.

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BRONCHIECTASIS[1]

Morphological Varieties of Bronchiectasis in Relation to History, Symptoms and Signs

JOHN CHAPMAN AND HENRY HOSKINS[2]

We have not been able to find in the American literature any detailed study of the relations between vareities of bronchiectasis and signs and symptoms associated with them. Bendove and Gershwin (2) most nearly produced such a study when they established six types of bronchiectasis as recognized from the bronchogram and attempted to correlate each of the types with a more or less specific type of aetiology and, to a certain extent, with symptom complexes. They gave no analysis of their figures, however. Other writers have largely been content to state that cylindrical bronchiectasis is a milder form than other varieties (1). Bronchosinusitic disease is generally recognized as a form of bronchiectasis and it is usually regarded as being relatively mild. Without attempting to correlate the types with the bronchogram, Brunn and Faulkner (4) state that their cases seem to fall into two types: one with a short and severe history dating from an attack of influenza, the other with a much longer history that includes attacks of bronchitis during childhood. To Shapiro and Jaches (11) bronchosinusitic disease seems to be relatively mild, while bronchiectasis in very severe form, in their experience, results from acute suppurative pneumonias.

Erb (6) describes an acute ulcerative bronchitis following which the pathological examination shows numerous transverse ridges along the course of the bronchi. The development of these ridges would naturally give rise to the beaded (8) or varicose (2) type. Graham, Singer and Ballon (8) find that influenza as a rule produces dilatations of the smaller branches.

Perhaps one reason for the paucity of comparable material is the fact that there have not been any generally accepted standards of nomenclature. Another is probably due to the fact that pure varieties are hard to find; whatever system of nomenclature one follows, he is pretty certain to find that his cases present a number of different kinds of dilata-

[1] From the State Tuberculosis Sanatorium, Sanatorium, Texas.
[2] San Antonio, Texas.

tion, although as a rule one type is predominant. It might even be suggested that types are not static but tend to develop one out of the other. Norris and Landis (10), for instance, state that the so-called varicose type is a variety of saccular, while the fusiform is a type of cylindrical bronchiectasis, an observation that seems entirely justified.

We have thought it worth while to study our series, comprising 116 cases, examined during the past three years up to April, 1939, to see if any definite relationships can be found between the aetiology as revealed by history, the symptoms and the signs and the type of dilatation discovered by bronchogram. In the discussion below, however, we are omitting from consideration 4 cases of fusiform bronchiectasis and 2 cases of bronchiolectasis as being too limited a series to permit scientific conclusions. All 4 cases of fusiform type were in women in the third and early fourth decades of life, a fact which could lead to unsound deductions.

For purposes of this study we have limited ourselves, therefore, only to the two well recognized cylindrical and saccular types, with the addition of the varicose, or beaded form. These three forms probably comprise the greater proportion of cases in any series and are sufficiently distinct in appearance that there should be no confusion in regard to nomenclature.

Even with all possible care to exclude bronchiectasis associated with tuberculosis, with definite abscess and with malignancy, it is difficult to be certain that these cases give more than an approximation of the true state of affairs. There is no account in any single history of atelectasis, which is certainly a factor of great importance in the development of bronchiectasis (3, 8). How many cases that were diagnosed as pneumonia had, in fact, the usual exacerbations of the disease is another unanswerable question. Even exhaustive questioning by the authors failed to lead to any satisfactory conclusions as to the true nature of the respiratory episodes mentioned, and we finally decided that perhaps we might be as safe in taking the attending physician's diagnosis as in attempting to analyze events of years past.

In table 1 we give the analysis of our patients in regard to type, sex and age. The ranges for age are approximately the same and there is no great difference in the means. It will be seen, however, that cylindrical bronchiectasis is about twice as frequent as either of the other two types which appear in about equal numbers. It is also evident that we discovered bronchiectasis in about two-thirds as many men as women,

which undoubtedly represents a statistical falsification, since in the sanatorium all patients fall in about the same ratio of sexes. It may also be commented that in the case of saccular bronchiectasis there are equal numbers of both sexes, but by statistical means (12), using the chi-square formula and a ratio of two-thirds as expected, one can show that for the number of patients considered this may be a result of chance. In the same way the divergence from two-thirds in varicose cases can likewise be shown to be insignificant.

Table 2 presents an analysis of symptoms in relation to types of dilatation; 49 patients, or not quite half, claimed never to have expectorated

TABLE 1

Sex and age distribution of 110 patients with bronchiectasis

TYPE	NUMBER	MALE	FEMALE	AGE RANGE	MEAN AGE
Cylindrical	60	23	37	16–59	39.9
Saccular	26	13	13	14–60	31.5
Varicose	24	8	16	15–59	36.8
Total	110	44	66		

TABLE 2

History of haemorrhage in 110 bronchiectatic patients

TYPE	NONE	STREAKED SPUTUM	FRANK HAEMOPTYSIS
Cylindrical	27	12	21
Saccular	8	5	13
Varicose	14	5	5
Total	49	22	39

blood at all, while 22, or 20 per cent, said they had brought up only blood-streaked sputum, and 39 admitted frank haemoptysis. These figures are fairly close to those of Lord (9) who reports haemoptysis in 50 per cent, Warner (13) who found haemoptysis in 45 per cent of 110 cases and Farrell (7) whose patients reported 42 per cent from a series of 100. It should be noted, however, that complete absence of blood-spitting is greater in proportion in cylindrical than in saccular or varicose types. If one assumes an equal distribution of haemoptysis and no blood, it can be shown by the same formula as used above that in saccular bronchiectasis the incidence of haemoptysis is significantly greater than in the other forms.

In regard to duration of expectoration we were able to get satisfactory approximations from 89 patients, of whom 37, or 42 per cent, gave a duration of five or more years. The distribution in the three types was not greatly different: a slightly greater number of each type had expectorated for less than five years than had for more than five years. In regard to amount of sputum, as estimated by the patient after being told household or familiar equivalents of ounces, quantitative estimates were given by only 63; 10 patients said they raised only slight amounts, but we discovered that their use of the term might mean anything. Of the rest, about half raised one ounce or less of sputum in twenty-four hours, and that figure holds roughly for cylindrical and saccular types, but in varicose bronchiectasis 10 patients produced less than one ounce daily, while 5 expectorated more than that amount. On statistical

TABLE 3

Duration of expectoration and age at which expectoration began in bronchiectatic patients

TYPE	ONE YEAR OR LESS	ONE TO FIVE YEARS	FIVE YEARS TO LIFE	PRIOR TO AGE OF TEN YEARS	FROM AGE OF TEN TO TWENTY YEARS
Cylindrical	12	12	19	8	7
Saccular	7	8	9	3	6
Varicose	4	9	9	5	3
Total	23	29	37	16	16

analysis with the chi-square formula, however, the difference from the expectation on the basis of the other figures is not significant.

In table 3 we attempt to break down the histories obtained to show the principal aetiological factors and their frequency. Forty-five of the total number of cases had no pneumonia at all, but 30 of these had cylindrical bronchiectasis; only 50 per cent of all patients with cylindrical bronchiectasis gave a history of pneumonia. In contrast with this, 77 per cent of patients with saccular bronchiectasis had the disease one or more times, and 63 per cent of patients with varicose dilatation had had the disease. Using the chi-square formula and taking a 50–50 distribution as in cylindrical bronchiectasis as the expected, we find readily that the difference in incidence between saccular and cylindrical bronchiectasis in regard to pneumonia as an aetiological factor is highly significant. No significant difference, on the other hand, can be shown between the incidence of pneumonia in varicose and cylindrical types.

In respect to influenza one finds that 33 per cent of patients with cylindrical, 15 per cent with saccular, and 25 per cent with varicose bronchiectasis denied the disease. Comparing the incidence in saccular with an expected incidence in cylindrical type, we found chi-square not to be significant. As in the case of pneumonia, it may be seen that there is no marked disparity of incidence of multiple attacks among the three varieties of patients.

In regard to nasal disease we found that but 38, or about 35 per cent, admitted having any type of disease of the nose or sinuses. While the patients with saccular bronchiectasis admitted a slightly high percentage of nasal involvement, there is no significant difference in the incidence of such disease. The figures in regard to abscess are too small to be worth consideration.

TABLE 4

Estimated amount of sputum in twenty-four hours in 110 cases of bronchiectasis

TYPE	30 CC. OR LESS	30–240 CC.	"SLIGHT"	MORE THAN 240 CC.
Cylindrical	14	15		4
Saccular	7	8		
Varicose	10	5		
Total	31	28	10	4

In table 4 we present miscellaneous comparisons among the groups. It is perhaps worth noting that almost 10 per cent of the patients with cylindrical bronchiectasis failed to present râles on physical examination. Noteworthy, too, is the fact that of the entire series only 10 gave either no definite history or a history of prolonged nasal and sinus disease alone. As might be expected from other writers' material, the overwhelming majority of these cases, 9, is found in the cylindrical type. Interesting, but not significant statistically, is the fact that 25 per cent of cylindrical types dated the onset of expectoration from the first two decades, while about 33 per cent of the other two types claimed that their expectoration started in the same period. In other words, only about 30 per cent of our patients dated the onset of their disease from the first two decades, while Farrell reports 54 per cent of his patients dating their symptoms from the first decade. Only 2 of the entire series had a positive serology for syphilis, while 4 patients claimed to have had asthma. All 4 were among the patients with cylindrical dilatations.

In regard to distribution of the lesions (table 5), we found that but 100 of our patients had received complete injection of both sides, and that, of this number, 39 had bilateral disease, 34 right lower and 27 left lower lobe involvement. Nine of those who had unilateral disease showed limitation to a few branches. In contrast with our figures one may consider those of Farrell who shows a much higher incidence in the left lower lobe only than in the right and those of Graham, Singer and

TABLE 5

Previous respiratory history of 110 patients with bronchiectasis

TYPE	PNEUMONIA				"INFLUENZA"				NASAL DISEASE	LUNG ABSCESS	NO DEFINITE HISTORY OR OF NASAL DISEASE ONLY
	Number of attacks				Number of attacks						
	0	1	2	3 or more	None	1	2	"Many"			
Cylindrical	30	12	8	10	20	18	12	10	19	2	9
Saccular	6	13	4	3	4	9	5	8	11	2	0
Varicose	9	8	2	5	6	5	6	7	8	1?	1
Total	45	33	14	18	30	32	23	25	38	5	10

TABLE 6

Distribution of bronchiectasis, according to lobes involved in 110 cases

TYPE	BILATERAL	RIGHT LOWER	LEFT LOWER	APPARENTLY LIMITED
Cylindrical	27	19	10	3
Saccular	6	4	13	1
Varicose	6	11	4	5
Total*	39	34	27	9

* The discrepancy between the totals in this table and the total number of patients is due to the fact that for various reasons 10 patients received injections on one side only.

Ballon who showed a slight preponderance in favor of the left lower lobe (5). There is very little difference in the three series in the incidence of bilateral disease (table 7).

In connection with the distribution of the lesion, however, it will be noted that the expected proportion of bilateral to unilateral disease in cylindrical types is about 50 to 50. Applying this figure to the figures we have for both varicose and saccular forms, we are able to show, by

means of the chi-square formula, that the figures for these two types are significantly different, that there is a significant tendency for varicose amd saccular bronchiectasis to be unilateral in comparison with the cylindrical type.

TABLE 7

Comparison of this with other series reported in the literature in regard to various factors in connection with bronchiectasis

SERIES	NUMBER OF PATIENTS	HAEMOPTYSIS	HISTORY OF PNEUMONIA	ABSCESS	MALE	FEMALE	NASAL DISEASE	BILATERAL	RIGHT LOWER	LEFT LOWER
		per cent	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*	*per cent*
Farrell	100	42	—	—	—	—	71	36	23	41
Lord	—	50	—	—	—	—	—	—	—	—
Warner	110	45	30	11	—	—	—	—	—	—
Graham	149	*	11.5	22†	50	50	—	44	23	27
This series	110	55.5	60	5	40	60	35	39	34	27

* Graham merely states that haemoptysis is more common in bronchiectasis than in tuberculosis.

† Is this marked difference due to the fact that we excluded all patients who presented X-ray evidence of abscess and relied merely on a history of previous abscess?

COMMENT AND CONCLUSIONS

1. We present a series of 116 cases, comprising 60 cases of cylindrical, 26 of saccular, 24 of varicose, 4 of fusiform and 2 of bronchiolectatic types of bronchiectasis. The last two types are disregarded due to their limited numbers.

2. Comparison of age and sex in the 3 principal types fails to show any marked differences. Although the ratio of women to men is 3 to 2, this represents about the proportion of the two sexes as admitted to the sanatorium.

3. It is found that our percentage of patients who give histories of blood-spitting is about that of other series reported. There is a significant difference in the incidence of blood-spitting between saccular and cylindrical bronchiectasis, tending to show that bloody expectoration is more common in saccular cases.

4. Of all patients, 42 per cent claimed to have brought up sputum for more than two years, and about half estimated their expectoration at one ounce or less in twenty-four hours. There were no significant differences in this regard among the 3 types.

5. About 40 per cent of our patients denied ever having had pneu-

monia, and about 50 per cent of the patients with cylindrical bronchiectasis denied the disease. The incidence of pneumonia in saccular bronchiectasis was significantly greater than in the cylindrical type.

6. Of all our patients, 27 per cent denied having had influenza and there was no significant difference in the incidence among the 3 types. Nasal disease was a complaint in 35 per cent of the series, but the incidence was about the same in the 3 varieties.

7. Cylindrical bronchiectasis failed to give physical signs much more often than the other types, just as a history either of no significance or related to the nose alone was found in the same variety. The only patients known to have asthma fell in the cylindrical group.

8. Our figures for distribution of disease differ from other reports in showing a relatively higher incidence in the right lower lobe as compared with the left. This is not what might be expected in view of the fact that congenital bronchiectasis should involve the left lower lobe more commonly (5).

9. We acknowledge that these studies are relative rather than absolute. Histories relating to the diseases of the respiratory tract are notoriously unreliable. We have also been forced to divide our cases arbitrarily into the 3 groups used, due to the polymorphism of bronchiectasis. Where one or more types of dilatation has been found, we have used the predominant type, leaning always to consider saccular as the diagnosis when it is present along with varicose or cylindrical forms, and varicose as the definitive type, if it is present in conjunction with cylindrical dilatations.

10. Within the limits of these methods, it appears that the distinction between cylindrical and saccular bronchiectasis is based on sound statistical grounds. Not so much can be said for other morphological types of bronchiectasis.

We are indebted to Dr. J. B. McKnight, Superintendent, for permission to use histories and charts in the possession of the Sanatorium.

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CLASSIFICATION OF CHRONIC BRONCHIECTASIS[1]

JOHN CHAPMAN AND DAVID McCULLOUGH

Although bronchiectasis has been a familiar finding at the autopsy table for many years and though the subject has become well known clinically within the last twenty years, there has not yet been offered a classification which has received general approbation and usage. Pathologists have been content to rest on a classification based on the two morphological varieties, cylindrical and saccular. The clinical classifications are most diverse and conflicting.

Shapiro and Jaches, Wasson and Ochsner make some effort to classify the disease on the basis of aetiology, distinguishing between that which results from sinus infection and attacks of bronchitis and that which results from other diseases. On a basis of history, Brunn and Faulkner have developed two types, one with a short history following influenza and the other with a much longer history usually dating back to repeated bronchitic episodes in childhood. Amberson divides his classification of acquired bronchiectasis into somewhat similar types. Andrus, on the other hand, if he is correct, does away with the question of aetiological classification altogether by maintaining that all bronchiectasis is the result of atelectasis.

Terms descriptive of the morphology of the dilatations are even more diverse. Bendove and Gershwin, for instance, consider bronchiolectasis and tubular, cylindrical, varicose, globular and primary bronchial abscess bronchiectasis as the basis of distinction. Graham, Singer and Ballon use such terms as grape, clubbing, cylindrical, saccular and beaded. Both groups of writers are almost alone in making efforts to correlate clinical and aetiological factors with morphology, the end toward which, it seems to us, all workers should be directing their efforts.

Having become dissatisfied with the various systems already in use, about two years ago we began to experiment with a classification that included all the important factors relating to bronchiectasis. Borrowing from all the previous systems and taking a hint from the American Heart Association, we arrived at the system set forth below. We have now

[1] From the State Sanatorium, Sanatorium, Texas.

used it exclusively at the State Tuberculosis Sanatorium for a year and have been much pleased by its inclusiveness. It is indeed true that, like the classification in use by the Heart Association, it is somewhat clumsy, but we have found that disadvantage offset by the character and conciseness of the information it offers.

CLASSIFICATION

I. *The Aetiological Factor*
- A. Congenital
- B. Primary Bronchiectasis (as described by David T. Smith)
- C. Acquired or Secondary Bronchiectasis
  1. Postpneumonic
  2. Postbronchopneumonic, reserved for the types that seem to be initiated by the bronchopneumonias associated with acute exanthems, pertussis, *etc.*
  3. Influenzal
  4. Postabscess
  5. Sinus-bronchitic form of Ochsner
  6. Mixed aetiology
  7. Bronchiectasis as a sequel to or in association with specific thoracic disease
     a. Tuberculous
     b. Fungus
     c. Malignant
     d. Silicotic

II. *The Anatomical Factor*
- A. As to morphology of dilatation
  1. Cylindrical
  2. Saccular
  3. Varicose
  4. Fusiform
  5. Bronchiolectasis
  6. Mixed forms
- B. As to location
  1. According to lobes, right middle, right lower, left upper, *etc.*
  2. According to bronchus, lingular, medial axillary, basilar, *etc.*, following the nomenclature of Pierce
  3. As to extent
     a. Diffuse
     b. Circumscribed
- C. As to degree of dilatation
  1. Slight
  2. Moderate
  3. Severe
- D. As to associated pathology
  1. With abscesses or cysts (This we have termed the lacunar type, which apparently is like Bendove and Gershwin's globular or Ballon's grape type.)
  2. With atelectasis
  3. With stenosis

III. *The Functional Factor*
- A. Symptomless
- B. Dry, haemoptoic (Sicard and Forestier)
- C. Mild productive
- D. Severe productive
- E. Septic

IV. *The Prognostic Factor*
- A. Progressive
- B. Nonprogressive
- C. As to health and life

It will perhaps be noticed that we omitted consideration of atelectasis as an aetiological factor. According to Boyd the loss of air from a lobe plus infection is a potent factor in the production of bronchiectasis, and it is only as a result of uncertainty as to whether to regard such post-atelectatic bronchiectasis as primary or secondary that we have omitted it for the time. There is also the fact that in our experience we have seen no patients who had ever been told they had atelectasis, the condition probably having been mistaken for abscess or pneumonia. Undoubtedly a place somewhere in the aetiological classification will have to be found for bronchiectasis resulting from massive collapse.

In listing the terms we use in describing morphology, we intentionally omitted from consideration Bendove and Gershwin's tubular variety, which they describe as "macaroni tubes." So far as we have been able to determine, this type is nothing more than cylindrical in which the tubes have been outlined rather than completely filled, a condition that is sure to happen when small or moderate amounts of oil are used. Sicard and Forestier so account for the type, describing the appearance as "ghost filling." We have also found it convenient to speak of "lacunar bronchiectasis" rather than of bronchiectasis with abscess or cyst formation.

For reasons well known to those familiar with bronchograms, no effort is made to distinguish between dilatations at different levels of bronchi. In nearly all cases dilatation begins with the largest branch and proceeds down to the smallest. In effect, fusiform bronchiectasis is descriptive of the rare condition in which the middle sized bronchi alone are dilated, while bronchiolectasis describes a dilatation limited to the small branches. Our varicose, taken from Bendove and Gershwin, probably corresponds with the beaded variety of Graham, Ballon and Singer.

The functional factor certainly deserves a place in the outline. In so

far as the patient's subjective feelings are concerned, it is by far the most important. It is but little less significant than an attempt to arrive at the prognostic factor. All these types are sufficiently familiar except perhaps the septic, our definition of which probably requires a little explanation. We apply the term to patients who characteristically block at intervals, with sudden elevations of temperature, chills, sweats and prostration, after which comes an unblocking and drainage with return to a more normal condition. This type is particularly prevalent among those patients who have an associated atelectasis or a partial stenosis.

It is needless to comment on the prognostic factor. In most cases we have not been able to satisfy ourselves as to whether the disease is progressive or not, due to the fact that they remain under our observation but a very short time. We have no alternative but to make a guess as to their chances for life and health, based, in part, on their previous history, in part on our clinical findings, such as quantity of sputum, course while in the hospital, appearance of ordinary roentgenogram and of bronchogram. Naturally, any prognosis must take into consideration one's view as to whether the disease is apt to progress, but in general he may be fairly safe in calling a mild cylindrical or a dry type nonprogressive.

We give below very briefly a few case reports illustrating the use of the system we advocate.

Case 1: S. H. E., white male, aged thirty-two, ill and expectorating at intervals since pneumonia at the age of eighteen. Had influenza in 1920, pneumonia also as an infant. Susceptible to "bronchitis" all his life. Had a haemorrhage three weeks before admission which led to diagnosis of tuberculosis for which he was sent to the Sanatorium. Bronchogram showed varicose dilatation of bronchioles of the left lower lobe. Diagnosis: postpneumonic bronchiolectasis; varicose, left lower lobe, diffuse; mildly productive; probably nonprogressive.

Case 2: A. N. J., white male, aged fifty-four, an oil field worker. Had influenza in 1918 and 1927, pneumonia in 1927. Expectorating a small amount for about three years. Previously treated as tuberculous and sent here with that diagnosis. Bronchogram showed cylindrical dilatation of all branches in right and left lower lobes. Diagnosis: bronchiectasis of mixed aetiology; cylindrical, right and left lower lobes, diffuse; mildly productive; probably nonprogressive.

Case 3: Mrs. R. D. B., white female, aged forty-four. Housewife. "Influenza" in 1918 and every winter since. Sinus and nasal disease for eight years. Blood-streaked sputum for eight years with recent definite haemorrhage. Has been raising about six ounces of sputum for the past year. Bronchogram: sacculations in both lower lobes. Diagnosis: sinus-bronchitic bronchiectasis; diffuse saccular, right and left lower lobes; moderately productive; probably slowly progressive. Outlook for life fairly good.

Case 4: A. W. A., white male, aged fourteen. History completely negative except for influenza in the early part of 1939. Had a six-ounce haemorrhage in 1935 and a smaller one this year. Sputum approximately 5 cc. in twenty-four hours for about a month. Bronchogram: advanced sacculations on the left with partial atelectasis. Diagnosis: bronchiectasis of undetermined aetiology; advanced saccular, left lower, with atelectasis; dry, haemoptoic type; probably will prove to be progressive or dangerous to health and life.

Case 5: H. A. J., white female, aged twenty-seven, an office nurse. Pneumonia at the age of two and seven. Empyema with rib resection in 1930. Pneumonia in 1939. Sinus disease with maxillary punch in 1930. (Related to empyema?) Claims she has expectorated for only three months. Mitral regurgitation. Has flare-ups with temperature of 102–3°F., chills and sweats. Bronchogram: sacculations, left, with partial stenosis and atelectasis, slight cylindrical dilatation in the cardiophrenic angle on the right. Diagnosis: postpneumonic bronchiectasis; saccular with atelectasis and stenosis diffuse left lower; slight cylindrical, limited to right lower lobe; septic; probably progressive and certainly dangerous to life.

These reports of quite markedly different cases serve to indicate the flexibility of this system. It has been our experience that it is sufficiently simple and yet adjustable to take care of the diagnoses of some hundred cases. We further believe that through some such systematic classification it will be possible to arrive at the correlation of anamnestic, aetiological, symptomatic and prognostic features with the morphological ones which we believe to be so important in the further study of the disease.

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COMPARISON OF REACTIONS TO DIFFERENT TUBERCULINS IN THE SAME INDIVIDUALS[1,2]

CHARLES L. SAVAGE

Several articles (1, 2, 3) in the recent literature have questioned the reliability of the tuberculin test when used as the sole index of tuberculous infection and have drawn attention to the variation in response obtained from different commercial preparations of tuberculin. The purpose of this report is to present the results of a study of the reactions of two groups of individuals to different preparations of tuberculin administered simultaneously or within short intervals.

Study A: A study was made in two colored penal institutions, the Virginia Manual Labor School and the Virginia Industrial School both of which are located in the central part of Hanover County, Virginia. The former institution receives Negro youths between the ages of twelve and twenty-four years. The latter receives Negro girls between the same age limits. The majority of the boys and girls are between the ages of thirteen and twenty. There are 322 individuals at the male institution and 115 in the female institution.

Only those individuals are included on whom all studies were completed. Five boys escaped during the study. No attempt was made to include inmates admitted during the study.

Procedure: A radiological examination of the chest was made on 322 males and 115 females by an X-ray unit, using paper films, supplied by the Powers X-Ray Company of New York. All questionable, positive and suspicious cases were X-rayed on conventional stereoscopic films. The roentgenograms were read by the author and Dr. E. C. Harper[3] without benefit of knowledge of the tuberculin reaction. Tuberculin tests were given to all X-rayed individuals while the films were being processed. Four tuberculin tests were given to each individual. A brand of Old Tuberculin, Purified Protein Derivative and the Vollmer

[1] From the Department of Preventive Medicine, Medical College of Virginia, Richmond, Virginia and the Hanover County Health District.

[2] Aided by a grant from the Dazian Foundation for Medical Research.

[3] Director, Tuberculosis Out-Patient Service, Virginia State Department of Health.

patch test from different manufacturers were administered simultaneously. Three weeks later a second brand of Old Tuberculin was used.

The Old Tuberculins and PPD were administered by the Mantoux method, giving .01 mg. as the first dose of OT and .000,02 mg. of PPD. If the first test was negative, a second one was given of 1 mg. of OT and .005 mg. of PPD. Each test was treated independently and repeated with second dose if negative, regardless of the results from other products. The Vollmer patch test material was applied after cleansing the skin with acetone. All tests were read after forty-eight hours and repeated at that time if necessary. In the Vollmer test the patch was removed after forty-eight hours; at this time a reading was made and another one forty-eight hours later. Readings were recorded according

TABLE 1

Tuberculin reactions to different preparations of tuberculin of 437 colored inmates of penal institutions between the ages of twelve and twenty-four years

	TESTED	FIRST DOSE REACTORS		SECOND DOSE REACTORS		TOTAL REACTORS	
		Number	Per cent	Number	Per cent	Number	Per cent
Test 1 (OT, Co. A)	437	187	42.8	75	17.2	262	60.0
Test 2 (PPD, Co. B)	437	88	20.2	115	26.4	203	46.5
Test 4 (OT, Co. B)	437	183	41.9	25	5.7	208	47.6
		48-HOUR REACTORS		96-HOUR REACTORS		TOTAL REACTORS	
		Number	Per cent	Number	Per cent	Number	Per cent
Test 3 (patch test)	437	106	24.2	68	15.5	174	39.8

to the criteria recommended by the National Tuberculosis Association in Diagnostic Standards (4).

There was a marked variation in the reactions of the group to the different products. Test 1 was apparently the most sensitive, whereas tests 2 and 4 had approximately the same percentage of total reactors. A comparison of tests 1 and 4 reveals that approximately the same percentage reacted to each of these on the first dose but that there were three times as many reactors to the second strength dose in test 1 as reacted to this dose in test 4. Test 2, on the other hand, elicited a positive reaction in only half as many on the first dose and had more reactors on the second dose then either of the Old Tuberculins. All positive reactors to test 3 were not revealed until the ninety-six-hour reading.

Among the 437 tested there were 274 reactors to one or more tests. The distribution of these reactors according to the tests to which they reacted is shown in tables 2 and 3.

A study of these two tables indicates that test 3 is less sensitive than the three tests which were given by the Mantoux method. The differ-

TABLE 2

Distribution of 274 reactors according to the number and type of test to which they reacted

Reacted to all four tests	166	
Reacted to three tests	26	
Test 1 (OT, Co. A)		26
Test 2 (PPD, Co. B)		26
Test 4 (OT, Co. B)		24
Test 3 (patch test)		2
Reacted to two tests	33	
Test 1 (OT, Co. A)		30
Test 2 (PPD, Co. B)		11
Test 4 (OT, Co. B)		21
Test 3 (patch test)		4
Reacted to one test only	49	
Test 1 (OT, Co. A)		40
Test 2 (PPD, Co. B)		—
Test 4 (OT, Co. B)		7
Test 3 (patch test)		2
Total reactors	274	

TABLE 3

Distribution of 274 reactors according to reaction to each test

	REACTORS		NONREACTORS	
	Number	Per cent	Number	Per cent
Total	274	100.0	—	—
Test 1 (OT, Co. A)	262	95.5	12	4.5
Test 2 (PPD, Co. B)	203	74.0	71	26.0
Test 4 (OT, Co. B)	208	75.9	66	24.1
Test 3 (patch test)	174	63.5	100	36.5

ences found in the other tests are open to two interpretations. One, that test 1 was more sensitive than tests 2 and 4; or two, that there are more nonspecific reactions to the product used in test 1 than for the other two products. The data are not of such a character as to indicate which of these explanations is the more probable.

Results of radiological examination: Of the 437 tested, the X-ray

examination showed possible tuberculous lesions in only 31, or 7 per cent. All but 5 of the 31 reacted to one or more of the tuberculin products and, of these 5, in 3 instances the radiological examination revealed only a pleurisy. In 3 instances active tuberculosis was revealed by X-ray,[4] all of these individuals reacted to all four tests. Twenty-two individuals were found to have calcium deposits, although 6 of these were deemed questionable. Twenty of the 22 with calcium deposits reacted to test 1, and each of the other 3 tests were positive in 17 instances. There was no evidence that any parenchymal lesion of clinical significance would have been overlooked by confining the X-ray examination to the positive reactors to any one of the four tests. On the other hand, each of the tests failed to produce reactions in persons

TABLE 4

Summary of the significant radiological findings with reference to the tuberculin reactions

X-RAY FINDINGS	OT, CO. A		PPD, CO. B		OT, CO. B		PATCH TEST		NEGATIVE	TOTAL EXAMINED
	.01 mg.	1 mg.	.000,02 mg.	.005 mg.	.01 mg.	1 mg.	Read 48 hrs.	Read 96 hrs.		
Calcium deposits	13	2*	4	9	13		6	7	1	16
Questionable calcium deposits	4	1*	1	3	4		3	1	1	6
Definite disease	3		2	1	3		2	1		3
Heavy trunks					1			1†		2
Pleurisy				1					3	4
Total										31

* Positive to 1 mg. OT, Co. A only.

† Positive to patch test only.

with evidence of infection as revealed by calcified lesions. The proportion of these nonreactors with healed lesions, however, was much smaller than reported by other observers (1, 2, 3).

Table 4 summarizes the X-ray findings with reference to the tuberculin reactions.

Study B: This group of individuals was composed of white children who had a familial history of tuberculosis. Their ages ranged from six

[4] Two of the positive cases were colored males ages sixteen and eighteen. The lesions were minimal in extent in both instances. The sixteen year old boy had a small fibroid lesion in the left apex. The eighteen year old boy had a small area of fibrosis in one apex with a small area of soft infiltration just off the root zone. The third case was a colored female with a small area of fibrosis in one apex. The final diagnosis was minimal tuberculosis in all three instances.

to twenty, with the majority between ten and sixteen. These children were sent in to the regular diagnostic clinics operated by the Virginia State Department of Health.

Each child was given two tuberculin tests simultaneously. The tests were administered in an identical manner as those in Study A. The letters A and B represent the same companies as represented in the study with the Negro group.

All positive reactors in this group had a chest X-ray film with conventional stereoscopic films. The shadows read as calcium deposits at this time are open to question in the light of later experience. Unfortunately, these films are not available for restudy.

The results of the testing of these individuals are shown in table 5.

The number of reactors to the first dose of each of these products was approximately the same. The difference in the total number of reactors

TABLE 5

Comparative reaction of 435 white contact children to simultaneous testing with two different tuberculin preparations

	TESTED	FIRST DOSE REACTORS		SECOND DOSE REACTORS		TOTAL	
		Number	Per cent	Number	Per cent	Number	Per cent
Test 1 (OT, Co. A).....	435	143	32.9	70	16.1	213	49.0
Test 2 (PPD, Co. B).....	435	135	31.0	37	9.6	172	39.6

is entirely due to the greater number of reactors to test 1 found by the second dose. While it is to be expected that the proportions reacting to tuberculin in this group of children would not be the same as found in the colored children, it might be expected that they would vary in a similar manner, namely, that test 2 would have fewer reactors to the first dose than OT, and the second dose of test 2 would have more reactors than the second dose of test 1. However, it is to be noted that approximately the same number of individuals reacted to the first dose of test 1 and test 2, and that approximately twice as many individuals reacted to the second dose of test 1 as compared to test 2. These facts are not identical with those from the Negro group where approximately twice as many reacted to the first dose of test 1 as did to the first dose of test 2, and one and one-half times as many reacted to the second dose of test 2 as to the second dose of test 1. The data are in agreement only in the fact that in both instances test 1 detected approximately 10 per cent more individuals than did test 2.

DISCUSSION

The outstanding observation in these studies is the variation in the number of reactors obtained with tuberculin preparations from different manufacturers. The fact that OT from Company A detected a significantly greater number of reactors than did any other preparation may be due to a more sensitive product or to the production of nonspecific reactions has been previously pointed out. No conclusion as to which is true is justified from the data presented.

Of the 3 tuberculin preparations administered intracutaneously, each detected a significantly greater number of reactors than did the patch test. Whether this increase in reactors represents greater specificity or nonspecific reactions again cannot be determined from this study.

Since 40 per cent of all the reactors to the patch test were not located at the end of forty-eight hours, but were found at ninety-six hours, the importance of reading at this time is clearly demonstrated.

It has been suggested (7, 8) that the patch test replace at least the first dose of tuberculin. In some instances, workers have found that it detected more reactors than did intracutaneous injections. These studies do not confirm these findings as a whole. There is one exception, namely, that the patch test detected all reactors to the first dose of PPD. Although it did detect the majority of the reactors from the first dose of other preparations, there is a possibility that among the remaining nonreactors to the patch test there might have been some who would have reacted violently to the second dose of OT or PPD. This study does not permit conclusion on this point.

The roentgenograms did not reveal a single significant lesion that would have been missed had only the reactors to any of the four preparations been X-rayed. Does this mean that the preparation with the least reactors is sufficiently sensitive to detect all clinically significant lesions? This question cannot be answered from these data. There are only five instances of tuberculous infections which were not detected by all tuberculin preparations and two of these were questionable.

SUMMARY

1. Four different tuberculin preparations from three different manufacturers have been compared in a group of Negro individuals. Two tuberculin preparations from different manufacturers have been compared in a group of white children.

2. Marked variation in the response to these preparations has been observed.

3. A greater number of reactors to one preparation has been demonstrated. Whether the greater number of reactors is due to greater sensitivity or production of nonspecific reactions cannot be concluded.

4. In so far as detecting clinically significant lesions is concerned, all preparations appear to be of equal value.

5. Further study of tuberculin preparations and the establishment of reliable standards for all commercial preparations are advisable.

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TUBERCULIN TESTS WITH OT AND PPD[1]

A Comparative Study of OT and PPD in Tuberculin Testing of Guinea Pigs in a Routine Diagnostic Service

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For many years it has been a routine procedure in our laboratory to tuberculin test all guinea pigs one month after the subcutaneous inoculation of material suspected of containing tubercle bacilli. For the test 5 mg. of OT, prepared from cultures grown on Long's synthetic medium, has been injected intracutaneously. Our records show that from 80 to 90 per cent of the animals that will develop tuberculosis will give a positive tuberculin reaction at one month after being inoculated with suspected material.

In 1936, we instituted, on all guinea pigs inoculated with material suspected of containing tubercle bacilli, comparative tests of OT and of PPD (purified protein derivative) developed by Long and Seibert (1, 2) which is claimed to be as specific as OT and which Long (3) has recommended for use as a standard tuberculin. The purpose of our study was to determine whether it might be advisable to discard testing with OT and to use PPD instead.

From the literature (3) one may judge that comparative tests on man of OT and of PPD have been adequately investigated. As might be expected, because of the difficulty of establishing uniform criteria for the presence of a tuberculous infection in man, the conclusions drawn by the various authors have not been in complete accord. Jensen *et al.* (4) found that there was a tendency for induration to be greater and for local tissue necrosis to be more frequent with OT than with PPD; other investigators concur in these findings. Since there does not seem to be any report in the literature on comparative tests of OT and of PPD on guinea pigs which have been inoculated to determine the presence or absence of tubercle bacilli, it may be of value to record the results we have obtained from 2,104 guinea pigs used in a routine diagnostic service.

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METHOD OF PROCEDURE

From practical experience we have found it advisable to use 5 mg. of OT when tuberculin testing guinea pigs. With this amount a very definite induration always occurs and local tissue necrosis frequently takes place if the reaction is positive. A strong reaction is of distinct advantage when guinea pigs with variegated markings are used.

At the time our study was begun we were unable to find any data relative to the comparative sensitivity of the guinea pig to OT and to PPD. From comparative tests of the two tuberculins on human beings, Long *et al.* (5) had reported that 0.005 mg. of PPD was as efficient as 1 mg. of OT in eliciting positive reactions and these authors had recommended 0.005 mg. of PPD as the maximum amount to be used in the tuberculin testing of man. We arbitrarily used 0.01 mg. of PPD in our guinea pig tests. This amount, theoretically, should be the equivalent of 2 mg. of OT, in so far as the reaction of man to tuberculin is concerned.

Later the work of Jensen *et al.* (4) showed that 0.002 mg. of PPD caused as great a local reaction in tuberculous guinea pigs as did 1 mg. of OT. On this basis 0.01 mg. of PPD should be the equivalent of 5 mg. of OT. It would seem, then, that the amounts of the two tuberculins used in our comparative tests should give relatively the same degree of local reaction, bearing in mind that in all tuberculin testing the results obtained are relative, not absolute.

The 2,104 guinea pigs in our series were divided into three groups. Group 1 consisted of 1,789 animals, which were inoculated subcutaneously with the concentrate from sputa, gastric contents, urine, pleural fluid or tissue and were given a tuberculin test one month after being inoculated. Group 2 was composed of 279 guinea pigs which had had a negative reaction to OT or to PPD, or to both, at the end of one month and were retested at the end of eight weeks. Group 3 contained 36 animals which were used in a special test of the effect of normal gastric juice on the viability of tubercle bacilli; these animals had a tuberculin test performed at the end of one month. Since we have yet to see a single instance of spontaneous tuberculous infection in the guinea pigs used in our laboratory, it was not deemed necessary to tuberculin test the animals prior to inoculating them.

RESULTS

In table 1 it is shown that of the 364 animals that reacted to OT only 300 reacted to PPD, *i.e.*, 17.5 per cent more reacted to OT than to PPD one month after being inoculated. Also it is to be noted that no animal gave a positive reaction to PPD and a negative to OT.

Of the 416 guinea pigs (table 2) which presented evidence of progressive tuberculosis on postmortem examination, 355 (85.3 per cent) had

reacted to OT, 295 (70.9 per cent) had reacted to PPD and 61 (14.7 per cent) had failed to react to either tuberculin when tested one month after being inoculated. Of the 64 animals that gave a positive reaction to OT and a negative reaction to PPD, 60 were positive and 4 were negative for tuberculosis on postmortem examination. In 5 instances there had been a positive reaction to both tuberculins with no evidence of progressive tuberculosis on postmortem examination. The positive tuberculin reactions in the 9 instances in which no evidence of progressive tuberculosis was found on postmortem examination could be interpreted as false positives; but, in 2 instances acid-fast bacilli had been observed in smears, and in a third, a culture of tubercle bacilli was

TABLE 1

Data on 1,789 routine guinea pigs tuberculin tested one month after inoculation

TOTAL NUMBER	BOTH OT AND PPD		OT POSITIVE, PPD NEGATIVE	OT NEGATIVE, PPD POSITIVE
	Positive	Negative		
1,789	300	1,425	64	0

TABLE 2

A comparison of the autopsy results with the tuberculin tests on 1,789 routine guinea pigs

TOTAL	GUINEA PIG		OT & PPD POSITIVE		OT & PPD NEGATIVE		OT POSITIVE, PPD NEGATIVE		OT NEGATIVE, PPD POSITIVE	
	Positive	Negative	Guinea pig positive	Guinea pig negative	Guinea pig positive	Guinea pig negative	Guinea pig positive	Guinea pig negative	Guinea pig positive	Guinea pig negative
1,789	416	1,373	295	5	61	1,364	60	4	0	0

obtained from the original suspected material. Therefore, it seems fair to conclude that none of these tuberculin reactions should be regarded as false positive.

Since 61 (14.7 per cent) of the tuberculous guinea pigs in group 1 failed to react to either tuberculin (table 2), it was of interest to determine whether such animals might give a positive reaction at a later date. In group 2 there were 275 animals that gave a negative reaction to both tuberculins and 4 animals with a positive reaction to OT and negative to PPD at the end of one month, all of which were retested with both tuberculins at eight weeks and then killed four weeks later. As shown in table 3, 19 of the 20 tuberculous animals in this group gave a positive reaction to both tuberculins on retesting, 15 had been negative to OT

and 19 negative to PPD on the first test, and the 4 animals positive to OT on the first test were positive to both tuberculins on retesting. One tuberculous animal failed to react to either tuberculin even on retesting. There were no positive tuberculin tests on animals without evidence of progressive tuberculosis on postmortem examination. This group of animals had been inoculated with concentrates from gastric contents, smears from the concentrates had been negative for acid-fast bacilli and the few positive cultures obtained showed very few colonies (one to three). With so few bacilli having been injected, it is evident that tuberculin sensitivity developed slowly in the infected animals, and it is probable that the 61 tuberculous animals with a negative tuberculin reaction at one month (table 2) present a situation similar to the positive animals in group 2.

TABLE 3

Data on tuberculin retest and autopsy findings of guinea pigs in group 2

TOTAL	TYPE OF TUBERCULIN	RESULTS AT FOUR WEEKS		RESULTS AT EIGHT WEEKS		GUINEA PIGS KILLED AT THREE MONTHS	
		Positive	Negative	Positive	Negative	Positive	Negative
279	PPD	0	279	19	260	20	259
	OT	4	275	19	260	20	259

Further confirmation that the 9 instances with a positive tuberculin reaction without evidence of progressive tuberculosis on postmortem examination (table 2) were probably not false positive reactions is found in the results of the study in group 3. Thirty-six animals were inoculated with concentrates from normal gastric contents to which tubercle bacilli had been added. The primary purpose of the study was to determine whether tubercle bacilli might be destroyed by prolonged contact with normal gastric juice. After the gastric content had been contaminated and thoroughly shaken, each specimen was divided into 3 equal portions which were kept in sterile containers at room temperature. At intervals of forty-eight, ninety-six and one hundred sixty-eight hours, one portion from each sample was concentrated; a smear, culture and guinea pig inoculation were made of each concentrate. In all of the smears acid-fast bacilli were readily demonstrated; cultures were positive in 33 out of 36 tests; a positive reaction to OT was obtained in 30 out of 36 and to PPD in 19 out of 36 animals. When postmortem examination was made six weeks after inoculation, 18 of 36 animals gave evidence of progressive tuberculosis.

It will be noted (table 4) that among the guinea pigs which gave evidence of tuberculosis on postmortem examination, a larger number had reacted to OT than to PPD, and among the animals which gave no evidence of tuberculosis on postmortem examination, a larger number had failed to react to PPD than to OT. Since it was known that each animal had been inoculated with tubercle bacilli and that only one-half of them showed evidence of tuberculosis upon postmortem examination, it is of particular interest to know whether the bacilli were viable at the time of inoculation. As noted above, a culture of each sample was made

TABLE 4

A comparison of tuberculin tests and autopsy findings in group 3, a series of 36 guinea pigs

TOTAL TESTS	TYPE OF TUBERCULIN	TUBERCULIN REACTION	GUINEA PIG	
			Positive	Negative
36	Ot	Positive	16	14
		Negative	2	4
	PPD	Positive	12	7
		Negative	6	11

TABLE 5

A comparison of culture and tuberculin reaction in group 3

TOTAL TESTS	TYPE OF TUBERCULIN	TUBERCULIN REACTION	CULTURE	
			Positive	Negative
36	OT	Positive	27	3
		Negative	6	0
	PPD	Positive	18	1
		Negative	15	2

at the time of the animal inoculation, so that it is possible to compare (table 5) the results of cultures with the tuberculin reactions produced in the respective animals.

Thirty-three of the 36 cultures were positive. The 3 instances in which the cultures were negative were from portions of gastric content that had been kept one week at room temperature. There were 11 such portions of gastric juice, 8 of which gave positive cultures. In table 5 it is shown that there is a closer correlation between positive culture and positive tuberculin reaction with OT than with PPD. In the 3 instances in which cultures were negative, the guinea pigs reacted to OT,

whereas only one reacted to PPD. These positive tuberculin reactions can hardly be regarded as false positive, even though the culture and guinea pig were both negative, since tubercle bacilli were demonstrated in smear preparations of the concentrates.

In the 18 instances in which the guinea pig showed progressive tuberculosis on postmortem examination, the culture also was positive; OT was positive in 16 and negative in 2, whereas PPD was positive in 13 and negative in 5. Of the 18 instances in which the guinea pig was negative, the culture was positive in 15 and negative in 3. And of the 15 instances with positive culture and negative findings on postmortem examination, 11 reacted to OT and 4 did not, whereas 5 reacted to PPD and 10 did not. From this study it would appear that OT is a more sensitive indicator than PPD in the amounts of tuberculin employed, and that a positive reaction to either product should not be considered false positive simply because the guinea pig failed to show evidence of progressive tuberculous infection.

The failure of one-half of the animals of group 3 to show evidence of tuberculosis at postmortem examination may be explained by the fact that the study was conducted in two parts, separated by about two months, and that different subcultures of strain H37 were used to contaminate the gastric contents. In the first part of the experiment, 15 animals were inoculated of which 11 developed progressive tuberculosis; in the second part, 21 animals were inoculated with only 7 showing tuberculosis at postmortem examination. A decrease of pathogenicity of the culture is suggested and indeed appears quite plausible, in that on several previous occasions subcultures of strain H37 have been found to be of very low pathogenicity for guinea pigs.

DISCUSSION

The primary purpose of our comparative study of OT and of PPD was to determine whether it might be advisable to replace OT by PPD in the tuberculin testing of guinea pigs, used to detect the presence of tubercle bacilli in a routine diagnostic service. It has been our experience, garnered from tuberculin tests on many hundreds of guinea pigs, that from 10 to 20 per cent of animals that have shown evidence of tuberculosis on postmortem examination have failed to give a positive reaction to OT when tested one month after inoculation; also, it has been a rare occurrence to have an animal that has shown a positive reaction to OT fail to show evidence of tuberculosis upon postmortem examination.

For PPD to be preferred to OT, a higher percentage of positive reactions at one month after inoculation and fewer positive reactions with negative postmortem findings should be obtained. The data presented in the text shows that 398 animals were positive to OT and 319 to PPD when tuberculin tested at one month after inoculation, a difference of 23.8 per cent between OT and PPD. Twelve animals positive to PPD and 23 positive to OT did not show evidence of tuberculosis on postmortem examination. Smears and cultures had been made from the material prior to the animal inoculation. Of the 12 animals positive to PPD and negative for tuberculosis on postmortem examination, 6 cultures of tubercle bacilli and 2 positive smears had been obtained from the original material; of the 23 similar instances in which a positive reaction to OT had been observed, 12 cultures of tubercle bacilli and 2 positive smears had been obtained. From the data presented, it seems reasonable to conclude that none of the positive reactions to either tuberculin was false positive. With the amount of tuberculin used, it is apparent that OT is to be preferred to PPD in the tuberculin testing of guinea pigs used in a routine diagnostic service.

The question may be raised whether comparable amounts of the two tuberculins were used. For tests in man, it is essential to use the smallest amount that will demonstrate a sensitivity to tuberculin; it is of importance to avoid local necrosis of tissue to gain the coöperation of the community, if for no other reason. From tuberculin surveys, Long *et al.* have found that 0.005 mg. of PPD gave as many positive reactions as 1 mg. of OT and, in their opinion, this is the largest amount one should use for intracutaneous tuberculin tests. In our tests on guinea pigs we have used twice this amount of PPD (0.01 mg.) and five times the amount of OT (5 mg.).

In determining the dosage of tuberculin to be used, it is a common practice to establish the standard for man by doing comparative tests on individuals who are known to be sensitive to tuberculin; the main reason for this is the general belief that tuberculin sensitivity in man and in tuberculous guinea pigs are not comparable. In such a situation it seems reasonable to accept, as a standard, comparative tests on the guinea pig when guinea pig sensitivity is under consideration. According to the investigations of Jensen *et al.*, 0.002 mg. of PPD caused as strong a reaction in tuberculous guinea pigs as did 1 mg. of OT. On this basis, the amounts of the two tuberculins used in our comparative tests are strictly comparable in the guinea pig.

We have found it desirable to tuberculin test guinea pigs used in a routine diagnostic service for the demonstration of tubercle bacilli for two reasons. First, a local induration may persist at the site of inoculation as a reaction to substances other than the tubercle bacillus. Secondly, palpable regional lymph nodes may not be present although a generalized infection may have developed. In the routine testing of the guinea pig there is no need to avoid local necrosis of tissue. As a matter of fact, a strong local reaction is to be preferred. It is our policy to read a tuberculin test negative unless there is a very definite local induration, with or without necrosis, forty-eight hours after the tuberculin is injected intracutaneously. In our laboratory we use animals with as great a variety of colors of hair as possible since the color and coat markings become a useful check in the identification of each animal. It is difficult to read tuberculin reactions in guinea pigs with dark skins except on a basis of palpable induration or tissue necrosis.

In our comparative study the local reaction to OT tended to be more severe than to PPD, local tissue necrosis being rare with PPD and common with OT, and a considerable variation in the intensity of the local reaction to OT has occurred. It may be argued that the difference in the reaction to the two tuberculins was due to the presence of nonspecific substances in OT. If one postulates that tuberculo-protein is the only specific substance in tuberculin, the presence of nonspecific substances in OT must be granted. It is doubtful, however, that tuberculo-protein is the only substance in tuberculin which can induce an allergic reaction. For instance, a tuberculin reaction may be elicited in an individual highly sensitive to tuberculin if he inhales the exhalation from a culture of tubercle bacilli. Tuberculo-protein unquestionably is a very potent constituent but it can hardly be regarded as the only specific substance in tuberculin. Perhaps the combined effect of the tuberculo-protein and other specific substances in OT have elicited stronger reactions than those produced by PPD because the latter contains the tuberculo-protein fraction only.

In this study the reaction to tuberculin was checked against smear and culture of the suspected material and postmortem findings on guinea pigs. An investigation of this type should afford a much more accurate analysis of the significance of tuberculin tests than is possible on human beings. The results herein reported may have a bearing on the significance of tuberculin tests on man.

SUMMARY

The results of comparative duplicate testing with OT (5 mg.) and with PPD (0.01 mg.) of 2,104 guinea pigs used in routine tests for the presence or absence of tubercle bacilli are presented. The tuberculin reactions were checked against smear and culture of the suspected material and postmortem examination of the inoculated animal. There was a difference of 23.8 per cent of positive reactions between OT and PPD in tests made one month after the animals had been inoculated. Retests at eight weeks on animals negative to both tuberculins at one month after inoculation showed no discrepancy between the two tuberculins. No false positive reactions to either tuberculin were proved. From the data presented it would appear that, in the dosage used, OT is to be preferred to PPD in the tuberculin testing of guinea pigs used in a routine diagnostic service.

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GASTRIC LAVAGE IN ADULTS WITH PULMONARY TUBERCULOSIS[1]

WILLIAM H. ROPER[2] AND WILLIAM H. ORDWAY

The examination of fasting gastric contents by smears for tubercle bacilli was first reported by Meunier (1) in 1898. This study was apparently overlooked until 1927, when Armand-Delille and Vibert (2) refocused attention on its importance. With the passage of time the examination by smear alone proved unreliable and the need for culture and animal inoculation was demonstrated (5, 10, 12, 17, 18). Since 1927 numerous articles have been published regarding the employment of this procedure in juvenile tuberculous patients. A complete review of the literature seems unnecessary since Gourley (3) has compiled an extensive bibliography. More recently the test has been used on adults and has been found valuable in establishing the diagnosis and in managing tuberculous individuals (4, 5, 10, 12, 14, 15, 17, 18, 19).

In May, 1936 we began studying the fasting gastric contents of tuberculous and nontuberculous patients. This report presents the findings obtained by guinea pig inoculations of these specimens for a three-year period.

The fasting gastric contents are withdrawn through a nasal tube into a glass syringe before the patient has taken any water by mouth and even prior to the usual morning oral hygiene. In obtaining the specimens we have followed procedures essentially similar to those described by Ulmar and Ornstein (4) and by Stiehm (5). At the same time we have observed those particular precautions emphasized by Belgorod and Schain (7), mindful of the possible pitfalls which might produce falsely positive results. When the fluid content of the fasting stomach is insufficient in quantity or unduly viscid in character, sterilized water is flushed back and forth through the tube by a syringe and the resultant admixture is added to the specimen. On several occasions, and without advance notice, rinsings from our equipment, samples of the mineral oil used for

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lubrication of the tube and specimens of the sterilized water have been tested by guinea pig inoculations with consistently negative results. All gastric specimens have been sent to the laboratory where they are digested and concentrated by centrifugation. Each concentrate has been examined by smear for acid-fast bacilli and by guinea pig inoculation and, more recently, by culture. As acid-fast bacilli have been present in a very small percentage of the smears, this report is concerned chiefly with the results of guinea pig inoculations.

NONTUBERCULOUS PATIENTS

During the three-year period of this study approximately 1,000 patients were admitted to the Sanatorium. Of these, 135 were diagnosed as having active pulmonary tuberculosis and the remainder were considered to be nontuberculous. Such a distribution afforded an excellent opportunity for using some of the nontuberculous cases as controls. Whenever gastric analysis has been done on any patient as a routine diagnostic procedure, the greater portion of the fasting or first specimen from the stomach has been concentrated and examined by smear and guinea pig inoculation for tubercle bacilli. These control tests were done concomitantly with those performed on patients who were known to have pulmonary tuberculosis, and specimens were often taken from tuberculous and from nontuberculous individuals on the same morning. Almost all of the gastric specimens in this control group were obtained within a few days after each patient's arrival at the Sanatorium, prior to establishment of the diagnosis.

Stereoscopic roentgenograms of the chest are taken on all patients on admission and additional films as indicated.

Consistently negative results were obtained with 264 specimens from 232 patients who were entirely free of tuberculous disease of the lungs according to history and by physical and roentgenographic examinations of the chest.[3]

Another group included patients without history or physical evidence of pulmonary tuberculosis but whose roentgenograms on admission were reported as showing parenchymal changes which were interpreted as "suspected" or "old healed tuberculosis of the lungs." For each pa-

[3] Since the compilation of this report, virulent tubercle bacilli have been recovered from the gastric contents of two patients whose roentgenograms were negative. In each instance, careful search of the upper respiratory tract has failed to reveal tuberculous lesions and subsequent observations have not demonstrated the development of parenchymal lesions.

tient this was simply an incidental finding. In each instance, subsequent clinical and roentgenological check-ups failed to indicate active pulmonary tuberculosis and all gastric tests on these patients were negative.

TUBERCULOUS PATIENTS

1. Results of Sputum Examinations: Prior to May, 1936, examinations of sputa by smear and/or inoculation into guinea pigs were the only laboratory procedures employed in this institution for demonstrating tubercle bacilli in material from the lungs.

TABLE 1-A

Two hundred and ninety-two patients with active pulmonary tuberculosis admitted 1926, 1927, 1928

		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
No sputum		30	68.2%	62	41.0%	12	12.4%	104	35.6%
Negative sputum	Smears − No guinea pig	6	8 18.2%	21	38 25.2%	5	10 10.3%	32	56 19.2%
	Smears − Guinea pig −	2		17		5		24	
Positive sputum	Smears + No guinea pig	5	6 13.6%	43	51 33.8%	72	75 77.3%	120	132 45.2%
	Smears − Guinea pig +	1		6		2		9	
	Smears + Guinea pig +	0		2		1		3	
Total		44	15%	151	51.7%	97	33.3%	292	

In the three-year period of 1926 through 1928, 292 patients with active pulmonary tuberculosis were admitted. Table 1-A demonstrates that positive recovery for the entire group was 45.2 per cent; for the patients with minimal disease, 13.6 per cent; moderately advanced, 33.8 per cent and far advanced, 77.3 per cent.

In 1933–1935, the three years immediately preceding the inauguration of this study, a rather different situation existed, as is shown in table 1-B. The proportional distribution of cases, by stages of disease, had shifted considerably. This change is explained largely by the fact that in recent

TABLE 1-B

One hundred and ninety-three patients with active pulmonary tuberculosis admitted 1933, 1934, 1935

No sputum		42	58.3%	32	33.3%	2	8%	76	39.4%
Negative sputum	Smears − No guinea pig	0		0		0		0	
	Smears − Guinea pig −	23	31.9%	22	23.0%	5	20%	50	25.9%
Positive sputum	Smears + No guinea pig	0		11		10		21	
	Smears − Guinea pig +	6	7 9.8%	19	42 43.7%	1	18 72%	26	67 34.7%
	Smears + Guinea pig +	1		12		7		20	
Total		72	37.3%	96	49.7%	25	13%	193	

TABLE 1-C

One hundred and thirty-five patients with active pulmonary tuberculosis admitted May, 1936 to May, 1939

		MINIMAL		MODERATELY ADVANCED		FAR ADVANCED		TOTAL	
No sputum		30	50.8%	20	32.8%	0		50	37.1%
Negative sputum	Smears − No guinea pig	0		0		0		0	
	Smears − Guinea pig −	19	32.2%	18	29.5%	1	6.7%	38	28.1%
Positive sputum	Smears − No guinea pig	1		12		10		23	
	Smears − Guinea pig +	7	10 17%	6	23 37.7%	0	14 93.3%	13	47 34.8%
	Smears + Guinea pig +	2		5		4		11	
Total		59	43.7%	61	45.2%	15	11.1%	135	

years fluoroscopic examinations of the chest (and roentgenograms when indicated) have been made prior to employment and as part of the

annual routine examinations of all employees at the Metropolitan Life Insurance Company's Home Office in New York City (8, 9); and more recently the same procedures have been followed at the Canadian and Pacific-Coast Head Offices. By such examinations the disease is more frequently recognized in its earlier stages. Beginning about 1933, all cases with sputum which was negative by smear examinations have been further tested by inoculation of concentrated sputum into guinea pigs. Yet, in spite of the increased usage of this more delicate test, the percentage of positive recovery for the entire group had fallen to 34.7 per cent; only 9.8 per cent in the minimal, 43.7 per cent in the moderately advanced and 72 per cent in the far advanced classifications.

For the three years beginning in May, 1936, findings by sputum tests approximated those obtained in the immediately preceding group. Table 1-C reveals positive recovery in 34.8 per cent of the entire group;

TABLE 1-D

Summary

Patients admitted with active pulmonary tuberculosis

PERIOD	SPUTUM				TOTAL
	None or negative		Positive		
	Number	Per cent	Number	Per cent	
1926–1928	160	54.8	132	45.2	292
1933–1935	126	65.3	67	34.7	193
May, 1936–May, 1939	88	65.2	47	34.8	135

for the minimal group 17 per cent, moderately advanced 37.7 per cent and far advanced 93.3 per cent.

Reviewing these three groups one observes that among the admissions to the Sanatorium the percentage of minimal cases has been almost trebled since 1929, while in patients with moderately advanced disease it has decreased slightly, and the proportion of those with far advanced involvement has declined to one-third of the former figure. Further, there has been no significant increase in the proportion of patients who were unable to raise sputum. Yet the percentage of positive sputum cases has fallen in spite of the more frequent usage of animal inoculation.

Table 1-D summarizes the findings in this triad of three-year periods on the basis of sputum examinations alone. In the first period, 45.2 per cent of all tuberculous patients exhibited positive sputum; in the second and again in the third period this figure was slightly under 35 per cent.

2. Results of Sputum Examinations Plus Gastric Lavage: Table 2-A portrays the detailed findings for the 135 tuberculous patients in the third group (table 1-C) on the basis of *all* tests that were done within four months after admission. We have shown that only 34.8 per cent of these patients gave positive recovery by sputum examinations alone. In summarizing, table 2-B reveals that the addition of gastric lavage to

TABLE 2-A

One hundred and thirty-five active tuberculous patients admitted May, 1936 to May, 1939
(Tests done within four months after admission)

			MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL
No sputum		Gastric guinea pig 0	4	2	0	6
		Gastric guinea pig −	14	3	0	17
		Gastric guinea pig +	12	15	0	27
Negative sputum	(Smears and guinea pig)	Gastric guinea pig 0	2	4	0	6
		Gastric guinea pig −	12	8	1	21
		Gastric guinea pig +	5	6	0	11
Positive sputum	(Smears +; sputum guinea pig 0)	Gastric guinea pig 0	1	12	10	23
		Gastric guinea pig −	0	0	0	0
		Gastric guinea pig +	0	0	0	0
	(Smears −; sputum guinea pig +)	Gastric guinea pig 0	3	1	0	4
		Gastric guinea pig −	2	1	0	3
		Gastric guinea pig +	2	4	0	6
	(Smears and sputum guinea pig +)	Gastric guinea pig 0	1	4	2	7
		Gastric guinea pig −	1	0	0	1
		Gastric guinea pig +	0	1	2	3
Totals			59(43.7%)	61(45.2%)	15(11.1%)	135

the armamentarium of laboratory procedures almost doubled the proportion of patients on whom positive recovery was obtained, *i.e.*, 63 per cent. This increase is due largely to positive guinea pig inoculations with gastric contents of those minimal and moderately advanced cases who were unable to expectorate; to a slightly less degree, to positive lavages from patients in the same groups who produced negative sputum.

Twelve patients with no sputum, or negative sputum, were not given

gastric lavage because they refused the test or left the Sanatorium prematurely. Excluding this group, on the basis that they were not adequately studied by all available procedures under discussion here, positive recovery was actually increased to 69.1 per cent in the 123 cases receiving *all* tests.

In the course of this study, 78 tuberculous patients were given gastric lavage during the first month of residence in the Sanatorium. Forty-three of these had no expectoration, and smear examinations of several sputa from each of the remaining 35 persons had been repeatedly negative. Eleven, or 14.1 per cent, of the 78 patients were subsequently found to be positive by guinea pig tests of the sputum; in 3 of these the stomach specimens were negative. Forty-four, or 56.4 per cent, were positive by gastric lavage alone. Thirty-six of these 44 patients were

TABLE 2-B

Total recovery by sputum and/or gastric lavage

SPUTUM OR GASTRIC LAVAGE	MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL
None or negative.....	32—54.3%*	17—27.9%†	1— 6.7%	50—37%
Positive.....	27—45.7%	44—72.1%	14—93.3%	85—63%
Total.....	59—43.7%	61—45.2%	15—11.1%	135

* 6 of these were not given gastric lavage.

† 6 of these were not given gastric lavage.

either not expectorating or were producing sputum which was consistently negative by microscopical examination and animal inoculation. In other words, by omission of lavage of the stomach, confirmation of the diagnosis would have been lacking in 36, or almost one-half of the 78 patients.

CONCOMITANT GUINEA PIG TESTS OF TWENTY-FOUR-HOUR SPUTUM AND FASTING GASTRIC CONTENTS

In an effort to compare the reliability and validity of sputum examinations with studies of fasting gastric contents, we have conducted a series of concomitant tests on tuberculous patients. Sputum was collected over a twenty-four-hour period, beginning early in the morning, followed by gastric lavage at the end of this period. Many of these particular studies were done on patients who had been under treatment for years and whose sputa had proved consistently negative by concentrated

smear examinations. Seventy-five such studies have been completed and table 3 presents the findings.

RESULTS OF REPEATED GASTRIC LAVAGES

On 35 tuberculous patients repeated gastric lavages have been tested on two successive mornings soon after admission. For these, the guinea

TABLE 3

Concomitant guinea pig tests of sputum and gastric contents
Seventy-five total trials on 54 tuberculous patients at any time during residence

	NUMBER TRIALS	PER CENT
Both negative	36	48
Both positive	18	24
Sputum guinea pig +; gastric guinea pig −	11	14.7
Sputum guinea pig −; gastric guinea pig +	10	13.3
Total	75	100.0

TABLE 4

Gastric guinea pigs on 174 active tuberculous patients in residence 5/8/36–5/4/39
Tests taken at any time during residence

		MINIMAL	MODERATELY ADVANCED	FAR ADVANCED	TOTAL		
		73	84	17			174
Only 1 gastric guinea pig	−	9	14	3	26	74.3%	35
	+	2	5	2	9	25.7%	
2 gastric guinea pigs	Both −	9	7	2	18	52.9%	34
	At least one +	3	10	3	16	47.1%	
3 or more gastric guinea pigs	All −	26	24	3	53	50.5%	105
	At least one +	24	24	4	52	49.5%	

pigs were both negative in 42.9 per cent and both positive in 34.3 per cent. In 22.8 per cent, the specimen obtained on one day was positive, while that of the immediately preceding or succeeding morning was negative by animal inoculation. Further investigations are now under way to determine the value of repeating the lavages on two and on three successive days in cases of early tuberculosis.

Table 4 gives the comparative results of single versus multiple tests on

174 tuberculous patients under treatment. The specimens in these groups were usually not taken on successive days. Further, they were obtained at any time during residence—often late in the course of treatment when it was less probable that they would be positive. One other factor affects the findings of this group, namely, that more repeated tests were done on those patients who had been negative by previous trials and continued negative results would be hoped for; however, in an appreciable number of these an unexpected positive status was demonstrated.

POSSIBLE INFLUENCES ON TUBERCLE BACILLI IN GASTRIC CONTENTS

Five hundred and seventy guinea pigs have been inoculated with concentrated gastric contents obtained from 174 patients with active pulmonary tuberculosis at any time during residence. Of these tests, 72.5 per cent were negative and 27.5 per cent were positive.

The content of regurgitated bile was roughly estimated by color of the fluids withdrawn from the stomach, and the specimens were tested for free hydrochloric acid by Töpfer's reagent. The presence or absence of bile in the specimens was found to exert no significant influence on the results of the animal inoculations. Bile was apparently absent in 307 specimens, of which 26.7 per cent were positive for virulent tubercle bacilli, and was present in 263, of which 28.5 per cent were positive. These percentages of positives are practically identical and closely approximate those for the entire series of tests.

Likewise, free hydrochloric acid does not appreciably alter the results. Ninety-six specimens failed to react to Töpfer's reagent, and 31.2 per cent of these were positive for tubercle bacilli; whereas 474 contained free hydrochloric acid, of which 26.8 per cent produced tuberculosis in the guinea pigs. An experiment conducted in the laboratory demonstrated that the viability of virulent human tubercle bacilli was not affected by free hydrochloric acid up to tenth-normal strength, even after forty hours of exposure and was only slightly inhibited after continuous contact with this strength of the acid for four days. Actually the normal fasting stomach usually contains free hydrochloric acid in strength of less than twentieth-normal—very rarely up to tenth-normal.

Regurgitation into the stomach of bacilli from tuberculous lesions of the intestine is highly improbable, due to the fact that tuberculous ulcerations rarely occur above the ileum. However, 93 patients were tested by gastric lavage and were also given X-ray studies of the gastrointes-

tinal tract. Of the 3 patients who showed roentgenological evidence of tuberculous enterocolitis, 2 had negative lavages and the third had a positive. On the other hand, 90 did not exhibit roentgenological evidence of intestinal involvement; 47 of these were negative by lavage and 43 were positive. Such X-ray examinations are done routinely on all patients who have advanced pulmonary tuberculosis and obviously a relatively higher percentage of positive gastric lavages is to be expected.

RESULTS OF SMEAR EXAMINATIONS

Up to August, 1939, 983 gastric concentrates were examined by smear for acid-fast bacilli and also inoculated into guinea pigs. In the hands of a specially trained observer acid-fast bacilli were found in 41 of the smears. The organisms were judged to have the morphological characteristics of tubercle bacilli in 28 of these specimens, of which 9 were from nontuberculous patients and were nonpathogenic for guinea pigs. The other 19 specimens which seemed to exhibit typical tubercle bacilli were from patients with clinical and roentgenological evidence of active pulmonary tuberculosis, yet 5 of these samples failed to produce tuberculosis in the experimental animals.

Thirteen gastric samples contained acid-fast bacilli which were morphologically atypical, 6 from nontuberculous and 7 from individuals on whom a previous diagnosis of tuberculosis had been proven; all of these were negative for tubercle bacilli by the guinea pig tests.

Of the 942 gastric concentrates that were negative by smear examination, 282 were obtained from nontuberculous patients and did not produce tuberculosis in guinea pigs. On the other hand, 660 had been withdrawn from tuberculous individuals and 157 of these proved to be positive by animal inoculations.

One must admit that the differentiation of acid-fast bacilli, by morphology alone, is very difficult for the average observer. One must further conclude, from the above findings, that the diagnosis of tuberculosis by smear examination is hazardous, even when done by an experienced technician.

Results of cultural methods are now being investigated. Thus far, 314 cultures have been completed on concentrated gastric contents, 46 of which were positive, while 54 guinea pig tests from the same group were positive.

DISCUSSION

In this report we have purposely made sharp and definite differentiation between sputum and fasting gastric contents for the sake of clarifi-

cation. Sputum refers to that bronchial secretion which is actually expectorated by the patient by coughing or clearing the throat. The so-called fasting gastric specimen contains that bronchial secretion which has gained entrance into the pharynx and has subsequently been swallowed. The swallowing of bacilli-laden sputum is admittedly dangerous and should be carefully avoided by all patients in so far as possible. Gastric lavage was initially employed in children because of their inability to expectorate. By means of this same test in adults, many positives are obtained among those whose conscientious efforts to raise sputum are unsuccessful, as well as in many of those producing unsatisfactory or negative sputum.

The procedure of obtaining the gastric specimen causes only slight discomfort to most persons and is not harmful; on the other hand, repeated forceful voluntary efforts to expectorate are uncomfortable and may be harmful. The importance of proving or disproving the clinical and/or roentgenological diagnosis of pulmonary tuberculosis is obvious; and of equal significance is the conclusive demonstration of the subsequent disappearance of tubercle bacilli from the bronchial secretions of tuberculous patients who are under treatment. Knowledge of these facts is surely of sufficient import to warrant and justify the use of lavage whenever it is indicated by the absence or negativity of sputum.

The validity of gastric lavage has been demonstrated by large numbers of negative controls and positive tests in our series; also in those of Stadnichenko and Cohen (10, 11) and of Kayne and Hounslow (12). The possible influences of several attendant factors in altering the results have been excluded, *viz.*, the presence or absence of free hydrochloric acid and bile in the fasting stomach and the complication of tuberculous enterocolitis.

Examination of the faeces has been suggested for the recovery of tubercle bacilli which have been swallowed. The collection of faecal specimens over a period of twenty-four or more hours is not simple, and the technical difficulties of digesting and concentrating such specimens are numerous. Faecal material might conceivably contain bacilli from ulcerative tuberculous lesions of the intestines, or from unsuspected involvement of the urinary tract which may produce contamination of the faeces, and thus give false positives in so far as the pulmonary process is concerned.

The study of the material obtained by laryngeal swabs has also been recommended (13, 14), as was originally reported by Blume in 1905 (16). This procedure entails mechanical scraping of the larynx with poten-

tially dangerous trauma to the laryngeal mucosa. It is "more reliable when irritation is exerted, sufficient to mechanically provoke sputum," as is emphasized by Menzel and Schramek (15). Theoretically the material obtained by such a method represents only a small amount of bronchial secretion which has accumulated over a brief period of time, while the fasting stomach should contain a larger amount of such secretion which has been amassed over a long period and is thus more likely to include bacilli, if and when they are present in the bronchi. For the same reason the method which employs the laryngeal mirror is probably less reliable.

Well known is the fact that sputum produced by the tuberculous patient may contain many tubercle bacilli on one day and none on the following day, or many in a morning specimen with none being raised in the afternoon of the same day. As shown above, in reporting repeated tests on newly admitted patients, we have demonstrated that the same variability occurs with gastric washings; and, in table 3, that concomitant examinations of expectorated sputum and stomach contents from a given patient may yield contradictory results, the one being negative while the other is positive. Levine (17) has reported similar observations. Further, the concentrates prepared from gastric specimens, as obtained from tuberculous patients in our series, were on several occasions halved, and two guinea pigs were inoculated for each gastric specimen. In one of these instances, one of the animals developed extensive tuberculosis while its partner remained entirely free of the disease as shown at sacrifice three months later! Stiehm (6) has emphasized the importance of repeated gastric lavages and recommends that the test be given on each of three successive mornings. He has found that only one or two of such repeated attempts on a given patient may prove successful in demonstrating the organisms. Gullbring and Levin (18) and Kayne and Hounslow (12) have reported similar findings. One must deduct that, with technique known to be careful and reliable, tubercle bacilli are often present in very small numbers and are frequently demonstrable only by repeated trials by all available procedures.

Gad (19) and others have obtained positive gastric lavages from a number of patients whose roentgenograms failed to reveal pulmonary tuberculosis, some of whom subsequently developed evidence of the disease by X-ray.[3] Trenis (20) finds lesions in the nasopharynx to be a source of tubercle bacilli when the roentgenogram of the chest is negative. Stiehm (6) reports positive lavages from a number of patients with

serous pleurisy which were previously thought to be nontuberculous. Menzel's (14, 15) studies failed to confirm these observations. In our present series there was only a single instance of such an occurrence. In one case, which was first thought to be convalescing from simple serous pleurisy, the roentgenograms of the lungs on admission were interpreted as suggesting but not definitely indicating parenchymal tuberculosis, and there was not sufficient pleural effusion to permit withdrawal for bacteriological study. One of the several gastric washings from this patient proved positive for tubercle bacilli.

Menzel and Schramek (15) attempted differential drainage of gastric content, duodenal fluid and bile, employing cultural methods for demonstrating the tubercle bacilli. They report that "in 40 cases of positive cultures, 5 were positive for gastric only, as against 18 for duodenal secretions, and 17 were so for both gastric and duodenal contents." From these observations they conclude that positive recovery is more likely from the duodenal fluids than from the gastric contents. Their series is small. Bacteriological differentiation of such specimens would seem to be hazardous, if at all possible. Fluid material from the stomach passes freely into the duodenum and often the reverse occurs. Furthermore, the tubes must be passed through the stomach into the duodenum without intervening sterilization. The results in our series indicate that regurgitation of bile into the stomach which necessarily involves the regurgitation of duodenal fluid does not affect the results obtained from gastric specimens.

CONCLUSIONS

1. With an extremely rare exception, and in the absence of tuberculosis of the upper respiratory tract, gastric washings produce tuberculosis in the guinea pig only when the donor has pulmonary tuberculosis.

2. Inoculation of the guinea pig with concentrated fasting gastric contents gives desirable proof that the tubercle bacilli are virulent.

3. By the addition of gastric lavage to examinations of sputum, positive recovery of tubercle bacilli was increased from 34.8 per cent to 69.1 per cent in 123 newly admitted tuberculous patients.

4. Gastric lavage is very important in those patients who do not expectorate, or who produce unsatisfactory or negative sputum.

5. This test is of assistance not only in the diagnosis but also in the management of the tuberculous patient. After years of treatment the sputum may disappear or become negative, while the gastric contents still exhibit virulent tubercle bacilli.

6. Several possible influences on the results obtained by gastric lavage have been excluded.

7. Diagnosis of tuberculosis on the basis of smear examinations is not dependable.

8. A single negative gastric lavage does not exclude active tuberculosis.

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PSYCHOLOGICAL FACTORS IN TUBERCULOUS PATIENTS[1, 2]

Observations at Sunnyside Sanatorium, with Especial Reference to Personality

IRVIN T. SHULTZ

In the rapidly accumulating literature on the subject of mental hygiene and its relation to tuberculosis, several points stand out. First: as far back as 1901 articles began to appear discussing apparent characteristic mental deviations in tuberculous patients. Second: there has been a tremendous increase in the attention given the subject in the last ten years. Third: hardly any two of the authors are in even approximate agreement on all points. Fourth: most papers seem to be based on casual observation rather than on scientific tests or accurately recorded observations.

It is safe to assume, however, that there are some distinct and definite mental aspects related to tuberculosis. Whether, as Munro (12) thought, there is a definite psychical state specific to and characteristic of tuberculosis with definite relations between the severity of the disease and the abnormality of the mental aspects, or whether, as Jones and Bogen (9) maintain, there is no mental or psychiatric inferiority among tuberculous patients and no differences that cannot be accounted for in terms of life "on the cure"—particularly sanatorium life—is beyond the scope of this paper. The fact seems established that the discovery that he has tuberculosis causes a mental shock of no mean proportions to even the best adjusted patient. His motives, desires and ambitions have been blocked, perhaps to even greater extent than his tissues have been impaired. While his body, ill with disease, must necessarily adjust itself to treatment which is hoped will restore it to normal, his mental and emotional life continues to function with the same intensity as prior to the onset of the physical impairment.

It is constantly becoming more generally recognized by the medical profession that mental therapy is nearly as essential as physical treatment and should accompany up-to-date methods of curing tuberculosis.

[1] From the Sunnyside Sanatorium, Indianapolis, Indiana.

[2] Publications, Indiana University Psychological Clinic, Series II, Number 26.

Physicians are thus becoming increasingly concerned with aiding the patient to readjust his mental and emotional life in order to hasten and supplement the physical cure. They know that fears and anxieties must be reduced to a minimum if the patient is to be restored to normal life. The mind and the spirit must be treated as well as the body.

Many sanatoria have therefore introduced occupational therapy, bedside teaching of academic subjects, radio schools and rehabilitation programs with beneficial results. The Marion County Tuberculosis Hospital, known as Sunnyside Sanatorium, located near Indianapolis, Indiana, has established such an education and rehabilitation program. During the academic year 1939–40, the Indiana University Psychological Clinic offered some psychological service integrated with the education department of the sanatorium.

Two main objectives seem to be indicated in a psychological program in an institution of this type. First: research in order to reveal facts and trends for future progressive building. Second: administering practical therapeutic aid to patients who request it. The following four-point program of investigation has been instituted.

1. Case history of each patient
   a. Previous vocation
   b. Educational background
   c. Socio-economic status
2. Vocational interests, aptitudes and skills
3. Personality inventory
4. Attitude of patient to own condition as it relates to future adjustment

Since no one escapes the habits, attitudes, ideals and predispositions of his early years, it is necessary to gather complete data on the case histories. Facts about previous educational, vocational and socio-economic background are essential. These are obtained through personal conferences, questionnaires and autobiographical sketches.

Vocational interests and aptitudes were determined by the Kuder self-scoring Preference Record. This located the interests and activities of the individual in one or more fields of economic endeavor.

The Pressey Classification and Verification Tests are used to determine the schooling and general educational level. Clerical abilities are tested by the Minnesota Test for Clerical Workers.

The patient's individual personality factors, the Bernreüter Personality Inventory attempts to measure by questionnaire methods. A knowledge of one's adjustment habits should be invaluable in self-analysis, both as to one's desirable and undesirable social patterns.

The fourth point is directed towards ascertaining, largely through personal interviews, the patient's attitude toward the future. What hopes, ambitions and plans does the future hold for the physically sick? Does the patient have a wholesome desire to participate again in normal activities of the outside world, or is he content to remain confined and inactive?

Such avenues of approach are being rewarded with a large mass of data, the analysis of which it is hoped will be valuable to the Sunnyside educational program as well as to the broader general problem of rehabilitating arrested tuberculous patients.

The remainder of the paper deals specifically with the results of the personality test which forms one part of the total program.

The Bernreuter Personality Inventory (19) was given to 82 men and 93 women at Sunnyside Sanatorium. This test attempts to measure six different aspects of personality as follows:

1. A measure of neurotic tendency (B1-N)
2. A measure of self-sufficiency (B2-S)
3. A measure of introversion-extroversion (B3-I)
4. A measure of dominance-submission (B4-D)
5. A measure of self-confidence (F1-C)
6. A measure of sociability (F2-S)

How do men and women patients at Sunnyside compare with the normal persons upon whom the test was standardized? Are they more variable? If, so, in what way and to what extent? Percentile norms have been worked out which enable a comparison between the scores given by the author and the scores made on the same tests by the men and women patients at Sunnyside.

(*1*) The neurotic tendency scale shows the emotional stability of the person tested. A high score indicates instability, and a low score indicates that the person is well balanced. The patients at Sunnyside proved more unstable emotionally than the general population. Of the Sunnyside group 76.8 per cent of the men (63) and 69.9 per cent of the women (65) exceeded the median of the standard group as given by Bernreuter.

Above the ninetieth percentile, which shows an extreme degree of neuroticism, there were 13.4 per cent of the men and 15.1 per cent of the women. These cases would benefit from psychiatric treatment. On the whole, there is a slightly larger percentage of neurotic men than women.

(*2*) The second test measures self-sufficiency. Persons scoring high prefer to be alone, rarely ask for sympathy or encouragement and tend to ignore the advice of others. Those scoring low dislike solitude and often seek advice and encouragement. The patients prove to be lacking in

self-sufficiency, the men more so than the women. In the Sunnyside group only 23.2 per cent of the men (19) and 33.3 per cent of the women (31) exceed the median of the Bernreuter group.

(*3*) A high score on the introversion-extroversion scale shows that the subject is introverted; that is, he is imaginative and tends to live within himself. The subject scoring low is extroverted; that is, he seldom suffers emotional upsets, rarely worries and rarely substitutes day-dreaming for action. The patients showed a greater than normal tendency toward introversion. Of the Sunnyside population 69.5 per cent of the men (57) and 73.1 per cent of the women (68) exceeded the median of the Bernreuter group.

(*4*) The fourth test is a measure of dominance-submission. Those scoring high tend to dominate others in face-to-face situations. Those scoring low are submissive. The Sunnyside patients are submissive rather than dominant. Only 24.4 per cent of the men (20) and 23.7 per cent of the women (22) in the Sunnyside group exceeded the median of the Bernreuter group.

(*5*) On the test which measures confidence in one's self, those scoring low are wholesomely self-confident and well adjusted to their environments. Those scoring high are hamperingly self-conscious and have exaggerated feelings of inferiority. The patients, as a whole, do lack confidence in themselves, are self-conscious and have exaggerated feelings of inferiority. Above the ninetieth percentile, which indicates the extreme condition of this kind, there are almost one-third of the men (31.7 per cent) and more than a fifth of the women (22.6 per cent). These cases can profit from psychiatric advice. Of the Sunnyside group 82.9 per cent of the men (68) and 77.4 per cent of the women (72) exceeded the median of the Bernreuter group.

(*6*) The sixth test measures sociability. Persons scoring high on this scale tend to be nonsocial, solitary and independent. Those scoring low are sociable and gregarious. The patients seem to be sociable and seek the companionship and friendship of others. Less than half tend to be solitary. Only 39.0 per cent of the men (32) and 40.9 per cent of the women (38) in Sunnyside exceeded the median of the Bernreuter group. This might be a compensatory reaction due to the patient's lack of self-confidence and self-sufficiency and because of their feelings of inferiority.

The norms of the Bernreuter Tests and the scores of the Sunnyside patients were compared further. Table 1 shows the means, the standard

TABLE 1

	BERNREUTER'S GROUP						SUNNYSIDE GROUP					
	B1-N	B2-S	B3-I	B4-D	F1-C	F2-S	B1-N	B2-S	B3-I	B4-D	F1-C	F2-S
Men												
Mean	−63.9	32.3	−28.4	53.9	−53.4	0.2	−23.7	7.9	−9.53	12.7	18.4	−16.11
Standard error of mean	4.56	2.84	5.06	3.29	2.69	1.83	7.7	5.40	4.85	6.51	8.86	5.30
Sigma or standard deviation	79.0	50.0	50.4	58.0	81.4	55.6	70.0	48.9	43.95	58.95	80.2	48.0
Number	300	310	99	311	914	914	82	82	82	82	82	82
Differences of means	40.02	24.40	18.93	41.20	71.80	16.31						
Sigma differences	8.90	6.10	7.00	7.30	9.25	5.60						
Critical ratios	4.51	4.00	2.70	5.60	7.76	2.91						
Women												
Mean	−27.6	3.2	15.8	18.4	1.0	18.8	0.40	27.52	8.80	17.04	55.40	31.10
Standard error of mean	4.08	2.96	4.15	3.27	3.09	1.87	7.11	5.38	4.28	5.16	8.02	5.49
Sigma or standard deviation	79.2	56.8	46.6	63.0	90.0	54.7	68.6	51.9	41.3	49.8	77.4	53.0
Number	377	367	126	371	848	848	93	93	93	93	93	93
Differences of means	28.00	30.72	24.60	35.44	56.40	12.30						
Sigma differences	8.20	6.13	5.96	6.10	8.58	5.79						
Critical ratios	3.41	5.01	4.12	5.80	6.57	2.21						

This table shows statistically the same results as by the method of per cents. The Critical Ratios; i.e., Differences of Means over Sigma Differences, are statistically significant, by standard formulae. See: *Garrett, Statistics in Psychology and Education*, 1937, Chapter VIII, Longmans Green Co., New York.

B1-N = Neurotic tendency
B2-S = Self-sufficiency
B3-I = Introversion—extroversion
B4-D = Dominance—Submission
F1-C = Self-Confidence
F2-S = Sociability

errors of the means, the standard deviations, the differences of the means, the sigma differences and the critical ratios for both men and women.

Bernreuter's group is less variable than the Sunnyside group, since the standard deviations are for the most part smaller. However, the differences as shown by the critical ratios are statistical significant and are not chance differences.

The men are more neurotic than the women, less self-sufficient, less introverted, somewhat more dominant and more lacking in self-confidence. Men and women are about equal in sociability.

Causal factors are probably to be found in more or less commonly expected childhood and adolescent problems of adjustment and habit formation, likely intensified by emotional shock and institutional con-

TABLE 2

Coefficients of correlation showing the relationship between the rank judgments of physicians and rankings of patients at Sunnyside on the Bernreuter Personality Test

MEN, NUMBER—82		WOMEN, NUMBER—93	
Trait	Correlation	Trait	Correlation
B1-N	+.105	B1-N	−.007
B2-S	+.123	B2-S	+.200
B3-I	−.034	B3-I	−.118
B4-D	−.013	B4-D	−.163
F1-C	+.113	F1-C	−.244
F2-S	+.001	F2-S	+.031

finement, rather than in the direct effects of institutional confinement and illness. These latter may play a more important part in some specific instances though.

CONCLUSIONS

Both men and women at Sunnyside are more neurotic, more lacking in self-sufficiency and self-confidence, more introverted, more submissive and more gregarious than the norms of the Bernreuter test would predict.

How well do the judgments of the physicians who care for the patients compare with the scores made by the patients on the standardized Bernreuter Tests? The physicians at Sunnyside were asked to judge the personalities of the patients on the six aspects of personality covered by the Bernreuter scales; *i.e.*, neurotic tendency, B1-N; self-sufficiency, B2-S; introversion-extroversion, B3-I; dominance-submission, B4-D; self-confidence,

F1-C; and sociability, F2-S. Each physician was asked to judge only the patients he personally attended. The physicians understood the purpose of the study and cooperated willingly. The coefficients of correlation are shown in table 2.

From an inspection of the table it is evident that the coefficients of correlation are very low, indicating that there is scarcely any relationship between the judgments of physicians and the ranks of the patients on the Bernreuter Tests. Since also the coefficients of correlation are consistently low, some even negative, it would seem that the physicians were in agreement among themselves in their judgments of patients. Evidently other factors not here discovered must account for the discrepancy with reference to the Bernreuter Test.

TABLE 3

Average rank on Bernreuter Neurotic Tendency Scale, B1-N, in relation to years spent in Sunnyside Sanatorium

YEARS IN SUNNYSIDE	MEN	WOMEN
1	68.48	29.25
2	74.60	25.21
3	83.71	41.35
4	72.11	55.66
5 or over	81.66	31.00

What is the effect of prolonged institutional life on the men and women of Sunnyside? An attempt was made to study the effect of the institutional life on the men as judged by a comparison of the number of years spent in Sunnyside with the average rank on the Neurotic Tendency Scale, B1-N. The available data show that there is apparently a slight tendency for men to grow more neurotic in proportion to the length of time spent in the sanatorium. This is especially noticeable after three years of confinement.

Women, on the other hand, seem to show a slight tendency to become less neurotic in proportion to the length of time spent in the institution until after two years. Then a slight increase is noted. However, so few cases have continued for this length of time that the results may not be reliable. It might also be well to mention that a considerably larger proportion of women than men leave against medical advice. Naturally, the more neurotic the patient, the more likely he is to resent confinement. Thus it may be reasonably assumed that there is a slightly greater

weeding-out of neurotic women than men, which may be sufficient to over-balance the normal tendency to grow more neurotic as the length of time at Sunnyside increases.

Table 3 indicates the years spent in Sunnyside for both men and women and the average rank on the Bernreuter Neurotic Tendency Scale, B1-N, in relation to years in the institution. The table can only be taken as indication of a trend as the cases are too few to insure reliability.

SUMMARY

A comparison of 82 male and 93 female tuberculous patients at Sunnyside Sanatorium, Marion County, Indiana, with norms of the Bernreuter Personality Test shows that the men are more neurotic than the women, less self-sufficient, less introverted, somewhat more dominant and more lacking in self-confidence. Men and women are equal in sociability.

Both men and women at Sunnyside are more neurotic, more lacking in self-sufficiency and self-confidence, more introverted, more submissive and more gregarious than the norms of the Bernreuter Personality Test would predict.

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STATISTICAL DATA

Edited by JESSAMINE S. WHITNEY

TUBERCULOSIS DATA FROM VARIOUS PARTS OF THE WORLD

Germany

The report[1] of the Imperial Tuberculosis Bureau for 1939–1940 gives a tuberculosis death rate, all forms, of 69 per 100,000 for the year 1937. In cities of 15,000 or more population, there has been a decline in the last three years, the rates being respectively 65, 59 and 58 per 100,000.

Cape Town, South Africa

The preliminary report[2] of the Medical Officer of Health of the City of Cape Town for the fiscal year ending June 30, 1940 gives a tuberculosis death rate of 242 per 100,000. Distributed according to European or non-European races, the rate for the former is 69 and for the latter 425 per 100,000.

Saskatchewan, Canada

The author[3] reports that in Saskatchewan only 39 per cent of patients discharged from sanatoria were well and working after five years, and that, in those patients who relapsed, overwork accounted for 29 per cent.

Oslo, Norway

The personnel of all primary schools in Oslo must be X-rayed yearly. Among 1,052 teachers, 1.1 per cent were affected; in 106 business school teachers, no case was found; among 406 school attendants (servants) 2.1 per cent, and in 105 "school hygienists" 1 per cent. The incidence among teachers is about the same as in the general population but that for attendants is considerably higher than the general rate.[4]

Lima, Peru

La Reforma Medica in its issue of June 1, 1940[5] gives some surprising figures regarding the place of tuberculosis as a cause of death in the city of Lima.

[1] Bericht Über das Geschäftsjahr 1939–1940, Reichs-Tuberkulose-Ausschuss.

[2] Annual Report of the Medical Officer of Health for the Year Ended June 30, 1940, The Corporation of the City of Cape Town.

[3] C. A. Wicks: The Post-Sanatorium Care of Tuberculous Patients in Ontario, Canadian Public Health Journal, 1940, *31*, 259.

[4] G. Hertzberg: Tuberkuloseundersokelsen av skolepersonalet i Oslo, Nordisk med., 1940, *6*, 985. (English summary)

[5] O. Téllez Sarzola: La mortalidad por tuberculosis en la Ciudad de Lima durante el quinquenio 1934–1938, La Reforma medica, June 1, 1940, no. 332, p. 351.

In the quinquennium 1934–1938, tuberculosis was the chief cause of death, averaging 1,313 deaths a year. Next came "other diseases of the respiratory system" with 822 deaths, and "diseases of the heart," which is the chief cause in the United States, averaging only 324 deaths a year. "Cancer and other tumors" reported only 285 deaths. Translated into death rates, the tuberculosis rate becomes 450 per 100,000, or nearly ten times the corresponding rate in the United States.

The author makes some valuable comparisons with other South American capitals as follows:[6]

CITY	TUBERCULOSIS DEATH RATE PER 100,000 IN 1936
Lima	462
Santiago	433
Rio de Janeiro	279
Panama	256
Montevideo	201
Bogota	137
Buenos Aires	136

And Lima is not alone in this high tuberculosis rate. The two other large cities of Peru, Callao (the port of Lima) and Arequipa, have equally high rates, in 1938 even exceeding that for Lima.

As in the United States, the tuberculosis mortality among men is higher than among women, and the greater number of deaths occur in youth and young manhood and womanhood. As in the United States, also, the greatest tuberculosis burden falls on the unskilled workers with the attendant poverty and deprivation.

Classified by race or color, the findings for Lima are as follows:

RACE	ANNUAL AVERAGE TUBERCULOSIS DEATH RATE PER 100,000 1934–1938
Indian	780
Mixed	630
Negro	350
"Yellow"	200
White	120

Continental United States

A recent release[7] from the Bureau of the Census, presenting provisional mortality figures for selected causes for the year 1939, shows a total of 61,609

[6] Figures taken from Epidemiological Reports, League of Nations, Geneva, 1938.

[7] Vital Statistics Special Reports, Bureau of the Census, Washington, D. C., December 17, 1940, *12*, 171.

deaths from all forms of tuberculosis and a rate of 47.2 per 100,000. These figures are somewhat higher than those released in our August issue (61,184 deaths and a rate of 46.6) as compiled from preliminary reports provided by State Departments of Health. Delayed death returns, reclassification of data and a revision in the population base for computing the rate bring about the change from the earlier report. The above figures of the Census Bureau are still subject to some revision, since they are provisional, but whatever difference there may be will be slight.

BOOKS

J. ARTHUR MYERS: *Man's Greatest Victory over Tuberculosis. Pp. x + 419, with 31 illustrations, Charles C. Thomas, Springfield, Illinois, 1940, cloth, $5.00.*

By WM. H. FELDMAN

The recent announcement by the United States Bureau of Animal Industry that bovine tuberculosis had finally been reduced to less than one-half of one per cent of the cattle in all of the more than three thousand counties of the United States, indicated that man had achieved almost a complete victory over a major disease that had been so firmly entrenched as to make its eradication seem to some a hopeless task. Fittingly, a well written account of how and why this was accomplished has been prepared by Doctor Myers.

The conquest of bovine tuberculosis was not accomplished in a brief span of time. The official eradication program began twenty-three years ago. Into the fight has gone inestimable physical effort, the careful planning by many capable minds, the untiring efforts of regulatory officials and the expenditure of a tremendous sum of public funds. To recount this story and emphasize the lessons learned that are applicable to the physician's attack on tuberculosis of human beings have been Doctor Myers's objectives. He has done the job exceedingly well and the result is a volume that should be in the possession of every physician and every veterinarian.

The book contains a pertinent foreword by Dr. John R. Mohler, Chief of the United States Bureau of Animal Industry, twenty-six separate chapters, a bibliography and an index. The scope of the book is large and embraces a discussion of the importance of cattle to civilization, a résumé of the evolution of the veterinarian, an historical account of the United States Bureau of Animal Industry, Quarantine and the Federal Inspection of Meats. Eight chapters are concerned more specifically with the biology of the tubercle bacillus, the diagnosis, treatment and pathology of bovine tuberculosis and immunity to the disease. Next follows a very complete discussion of the bovine type of tuberculosis in man in which the controversy provoked by Koch's opinions is reviewed as is the literature supplying the evidence that no longer permits even a reasonable doubt as to the ability of the bovine tubercle bacillus to affect human beings. This chapter which should be of especial interest to the pathologist also contains several excellent illustrations of the lungs of human beings with lesions of tuberculosis caused by bovine tubercle bacilli.

Seven chapters are devoted to the efforts to protect man against bovine tuberculosis and a description of the methods that finally succeeded. Following a chapter on tuberculosis in animals other than cattle, the text terminates with an impressive essay concerning the value to physicians of the experiences gained by veterinarians in controlling tuberculosis of cattle.

A unique and valuable feature of the book are the summaries that close the respective chapters.

Doctor Myers's book is a great tribute to the veterinary profession for having accomplished so much against such a formidable enemy. His ability to collect, organize and integrate data is well reflected in this, his latest book. As usual he writes with clarity and with the enthusiasm and conviction that characterizes the crusader. The result is a volume that may be read for the sheer pleasure of the experience or which may be consulted as an authoritative source of valuable information.

The publishers have done a workman-like job in producing a well-bound, attractive volume.

J. B. McDOUGALL: *Tomography. Pp. 73, with 110 illustrations, London, H. K. Lewis & Co. Ltd., 1940, fabrikoid, 21s.*

By ELI H. RUBIN

The present monograph is a timely presentation of a subject which is receiving increasing attention by roentgenologists and physicians interested in chest diseases. Tomography or sectional radiography allows one to study serial layers of the lungs and other parts of the body with a minimum of interference by overlying structures. Inasmuch as in chest radiography the ribs obscure about two-thirds of the lung parenchyma and the scapulae, muscles, breasts and other elements contribute greatly to the further diminution of lung translucency, it is quite understandable why a modality which enables one to examine the lung in sections, approximating in life what the pathologist does with his dissecting knife, should appeal to physicians.

Following a concise presentation of physical principles and technical details in tomographic examination, the author presents the finished product on fifty-six pages containing one hundred and ten illustrations. Explanatory notes are adequate and make for easy grasp of the subject. On page 63, the word "korrectorplasty" was probably a misspelling rather than poor English. In all other respects, the monograph made enjoyable reading. The major part of the work is devoted to the use of tomography in the diagnosis of pulmonary tuberculosis with special regard to the visualization of cavities in collapsed and noncollapsed lungs. The fact that in many instances shown one would have diagnosed cavitation on other grounds does not minimize the importance of seeing the cavity at a fixed level in the lung, particularly when

operative treatment is contemplated. The few pages devoted to the use of tomography in the diagnosis of bronchial stricture caused by neoplasm, obtained from the late Dr. E. W. Twining's collection, should stimulate further study of this subject as well as of other nontuberculous diseases.

Doctor McDougall might have devoted a few pages to a description of one or two "home-made" contraptions which serve the purpose equally well as the more expensive apparatus. Many institutions and physicians are installing the former at a very small cost.

WILLIAM H. HOLMES: *Bacillary and Rickettsial Infections, Acute and Chronic. Pp. 676, New York, The Macmillan Company, 1940, cloth, $6.00.*

By MAX PINNER

This is a unique textbook, unique in purpose, arrangement and style. Its central purpose is to convey an understanding of the diseases discussed; the specific teaching of diagnosis and treatment is a subordinated aim. Each disease is presented as a complete entity in which historical importance, the historical development of its study, epidemiology, immunology, bacteriology and pathology are given the emphasis that they deserve from the point of view of a full understanding and not only from the point of view of the practicing physician who is called upon to diagnose and treat the particular disease in an individual patient. This entails a shift of emphasis from diagnostic and therapeutic technique to those fundamental aspects that are in the majority of textbooks discussed in small type—actually or figuratively. Each disease is shown as the community problem it is and in its rôle that it has played in the development of civilization against a background of and interwoven with pertinent socio-economic conditions.

The style is that of a cultured racconteur, graceful and eminently readable. The result is a book that combines consuming interest and esthetic pleasure. In spite of many necessary quotations and citations from the literature, the book carries strongly and consistently throughout the individual stamp of its author; it is the impression of this reviewer that this applies not only to the particular type of arrangement, as pointed out above, but to the contents as well. This is not a "strictly objective" textbook whose contents could be passed without dissent and criticism by all teachers in the respective fields. Scientific objectivity is well tempered by the considered subjective judgment and opinion of the author; it is not an aloof, encyclopedic presentation of facts, rather a lively organic structure whose building stones are facts (that can be found in rather scattered fashion in many another textbook) and whose cement is matured and balanced interpretation and integration (that are so rarely found in current textbooks).

Doctor Holmes' book, besides its informative value, presents a profoundly interesting and probably highly successful method of teaching. Both tyro and experienced physician will undoubtedly learn from and thoroughly enjoy it.

(Dr. William H. Holmes' death was announced on November 2, 1940.)

E. V. McCollum and J. Ernestine Becker: *Food, Nutrition and Health. Fifth edition. Pp. v + 127, McCollum and Becker, Baltimore, 1940, cloth, $1.50.*

By S. BILOON

This book is planned to present in simple nontechnical language the established facts about nutrition. It is designed to inform the intelligent layman of the importance of food and nutrition in the promotion of good health. It will also serve to keep properly oriented the physician whose interests are not directly concerned with these matters.

The text is clear and readable. Some of the most popular fallacies about food and personal hygiene are discussed and a sound basis for understanding is established. Especially commendable is the excellent chapter on the Dietary Habits of man.

This book is recommended very highly to the educated layman and physician.

Philip P. Jacobs: *The Control of Tuberculosis in the United States. Revised edition. Pp. 387, National Tuberculosis Association, 1940, cloth, $2.00.*

By CHARLES J. HATFIELD

The latest edition of Philip Jacobs' book *The Control of Tuberculosis in the United States* is a most important and valuable addition to the library of any worker in public health. It has been almost wholly rewritten and presents the most complete record available of the development and techniques of the most important and successful voluntary association, working in the field of public health, in the world. Since many methods outlined in the record are applicable to other fields of community health and welfare, the book is certain to be of use to many students and executives.

Doctor Jacobs entered the field with unusual qualifications. His educational background was very good, and his early training in journalism was valuable. His enthusiasm and energy were always available, and his devotion to the fight for the control of tuberculosis was evident at every stage of his development.

Part 2 of the volume, which deals with methods for educating the public, qualifications of personnel, fund raising and relations with other welfare

agencies, both official and voluntary, is especially valuable, and is based on the author's experience of more than thirty-five years. The discussion of programs for the control of the disease, elastic in essentials to fit any geographical area, are also most helpful. Perhaps the most valuable quality of the book is the insistence on coöperative effort between all the agencies that are actively engaged in any phase of the medical and social fields relating to tuberculosis. If the goal of control of the disease is to be reached, every agency must actively participate.

The volume is most timely. All have reason to be thankful that Doctor Jacobs was able to record his knowledge of the development of antituberculosis work before the illness that led to his untimely and lamented death.

RAYMOND PEARL: *Introduction to Medical Biometry and Statistics. Third edition, revised. Pp. xv + 537, W. B. Saunders Company, Philadelphia and London, 1940, $7.00.*

By GEORG WOLFF

The new edition of the well-known introduction to medical statistics came out just a few months before the author's unexpected death. The fact that a third edition of a statistical textbook could appear after a relatively short interval may be taken as an indication that the introduction has served its purpose very well and has in the meantime acquired many new friends. It is something intermediate between a purely mathematical treatment of statistics and an elementary textbook of statistics. "The primary aim of this revision has been to make the book still more useful to beginners in biometric and statistical work, particularly in the fields of medicine and public health," the late author wrote in his preface. One of the introductory chapters especially worth reading deals with some landmarks in the history of biostatistics from John Graunt's famous *Bills of Mortality* (published in 1662) up to the achievements of Francis Galton in eugenics and Karl Pearson in mathematical statistics who were indeed the founders of modern biometry and its application in medicine and general biology. They attracted a great many students and scientists from all over the world, of whom the young Raymond Pearl was one. Further chapters treat the tabular presentation of statistical data, their graphic representation, rates and ratios (birth rates, death rates, morbidity rates, death ratios or proportionate mortality rates). However, the logical distinction between rates and ratios is not always very definite. The life table technique and the great importance of this method for the evaluation of pure mortality rates and life expectation are explained *in extenso*. The author indulges perhaps here a little too much, for a statistical textbook, in his own

work regarding the construction of life tables for lower animals (Drosophila, etc.) which, however, may have some day a great importance for comparative biology. Another chapter deals with the important matter of sampling error (probable error and standard error) and the determination of statistical significance of observed differences. There are some more chapters dealing with elementary theory of probability and some more special theorems and their practical application (Chi-square test in "Goodness of Fit"), the measurement of variation and correlation, simple curve fitting and at close the so-called logistic curve, another favorite research subject of Pearl's to find a special formula for a curve describing best the present and future growth of human and animal populations. This formula was developed in 1920 by Pearl and Reed and has found more or less general recognition in population theory. All in all, Pearl's book will be again a very useful help in statistical research, giving something more by its personal note than a pure textbook in statistics. It is furthermore a lasting memory of Raymond Pearl indefatigable, until his premature death.

CHARLES C. PETERS AND WALTER R. VAN VOORHIS: *Statistical Procedures and Their Mathematical Bases. Pp. xiii + 516, McGraw-Hill Book Company, New York and London, 1940, $4.50.*

By GEORG WOLFF

This is a new textbook on statistical methods including the mathematical derivations of the most frequently used statistical formulae. It has not the personal character of Pearl's above mentioned introduction but it is the textbook proper for everyone who wants to go more deeply into the statistical procedures and principles of modern research work. "We believe," the authors state, "that, if statistical workers do not take their tools as magic but understand them in the light of their origins and assumptions, they will use these tools more intelligently and more safely." Therefore, they always give the derivations in much detail and they open, moreover, the book with a short chapter on calculus that is readily understandable and makes the following chapters easier to understand. On the other hand, this clearly demonstrates the character of the book. It is not especially written for use in biological research but it might be, together with a book like Pearl's, a great help in giving a thorough knowledge of more advanced statistics. In the single chapters the measurement of variation and correlation, the reliability of statistics considering the different errors of the obtained values, higher correlation and regression formulae, the normal probability curve, the computation and application of Chi square are dealt with and some more specialized items of

modern statistics. Here the authors follow in particular R. A. Fisher who, as successor of Karl Pearson, has had the greatest influence upon the development of present statistical methods, especially in the biological sciences. Whether they have succeeded "to take the magic out of them," however, will depend in the first line upon the reader himself. If he takes the time to go carefully through all the steps, as is necessary in comprehending complicated methods, he will beyond doubt welcome the new textbook as a reliable guide. It might finally be suggested for a new edition, that is likely to come out soon, to add some more practical examples of computation from different field works instead of giving too much space to the mathematical formulation.

Books Received

M. BENMOSCHÉ: A Surgeon Explains to the Layman. With foreword by Dr. Howard Lilienthal. Pp. 317, Simon and Schuster, New York City, 1940, cloth, $3.00.

BENJAMIN ENQUIN AND JUAN ALBERTO AGUIRRE: La radiografia penetrante del torax. Pp. 145, with 103 illustrations, Editor El Ateneo, Buenos Aires, 1940, paper.

R. B. HILL AND E. I. BENARROCH: Anquilostomiasis y Paludismo en Venezuela. Pp. 204, Publicaciones del Ministerio de Sanidad y Asistencia Social, Caracas, 1940, paper.

LUIS SAYÉ: Doctrina y practica de la profilaxis de la tuberculosis. Pp. 355, with numerous tables, charts and figures, Editorial Sudamericana, S. A., Buenos Aires.

CHARLES WEYL, S. REID WARREN, JR. AND DALLETT B. O'NEILL: Radiologic Physics. Pp. xvii + 459, with 166 figures, 1941, Charles C. Thomas, Springfield, Illinois, cloth, $5.50.

Quinto Congresso Pan Americano de la Tuberculosis—Buenos Aires—Cordoba, October 13–17, 1940. Pp. 527, with many figures, tables and charts, Editor El Ateneo, Buenos Aires.

Transactions of the Association of American Physicians. Fifty-fifth Session, held at Atlantic City, New Jersey, May 7 and 8, 1940. Pp. xl + 324, Philadelphia, Printed for the Association, 1940, fabrikoid.

Philip King Brown
1869–1940

With the 49'ers in California, there arrived a Minister, Missionary and Army Chaplain, shortly to be followed by his family. His daughter, Charlotte, was destined to become the pioneer outstanding woman physician in California. This was the mother of Philip King Brown.

Born in the fertile Napa Valley of California in 1869, he soon moved with his family to San Francisco. Following a preliminary education, Philip King Brown received his A. B. from Harvard College in 1890, followed by his M. D. in 1893. In 1895 and 1896 he traveled abroad, doing postgraduate work in medicine at Berlin and Göttingen, and spending some time in Paris and London. Upon his return to San Francisco, his keen intellect and enquiring mind, combined with an energetic personality and supplemented by the background of information acquired during these well-applied years in the medical centres of the world, gained early recognition by his medical associates.

In March 1900, he married Helen Adelaide Hillyer, who survives him. This marriage was blessed by four children: Hillyer, Bruce, Cabot and Phoebe. His wife has been by his side during all these years in fact, as well as in spirit. To create the proper atmosphere in the home of a busy practitioner of medicine, to remove as much as possible the annoyances and cares of daily living, to guard jealously of his time, to further his ambitions, is no mean task. All this was well consummated in the Brown household.

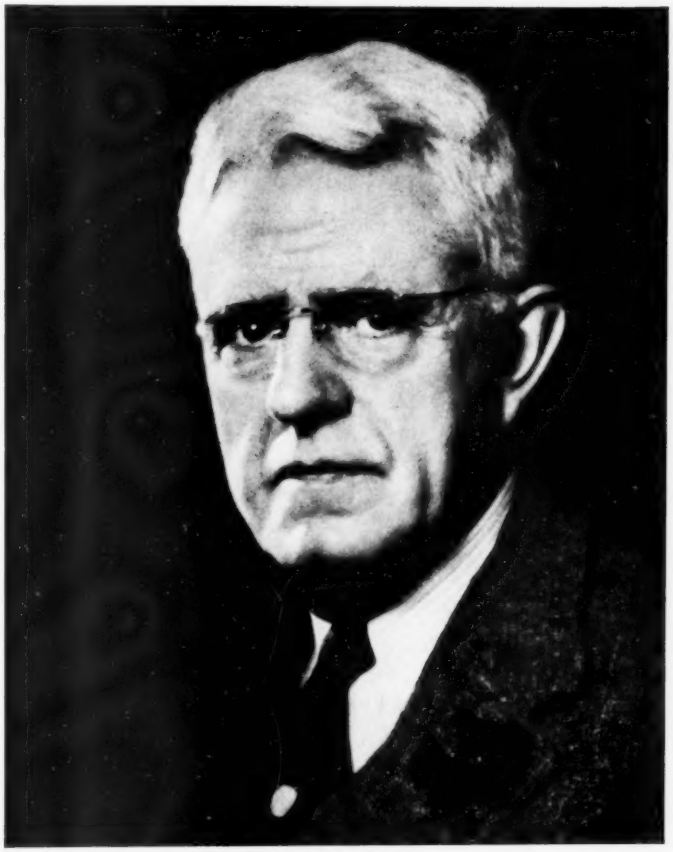
Philip King Brown's interest covered many fields of medicine, as well as allied technical, social and civic problems. The bibliography of his writings is indeed a long one.[1]

Among other things, his interest in tuberculosis led him to organize Arequipa Sanatorium, situated at Manor, in the beautiful hills of Marin County across the Bay from San Francisco. This sanatorium was designed for, and in fact is, an institution to aid young working women

[1] Dr. Philip King Brown was probably the first author to have described in some detail a case of agranulocytosis, under the title *A Fatal Case of Acute Primary Infectious Pharyngitis with Extreme Leukopenia*, American Medicine, 1902, *3*, 649. (Editor)

overcome their tuberculosis and achieve again a normal life. Doctor Brown was the Medical Director for seventeen years and continued as Secretary of the Board of Directors.

He has at various times furthered his deep interest in medical education by teaching in the University of California Medical School and the



Philip King Brown
1869–1940

Stanford University Medical School, both in San Francisco. From 1920 to 1939, he was supervisor of the Medical Service at the Southern Pacific Hospital. This large amount of medical material was used not only primarily for the benefit of the patients themselves, but for teaching and to obtain therapeutic and statistical information for the advancement of medical knowledge.

Feeling the need of a private institution for the care of private patients with tuberculosis and allied diseases, Doctor Brown, in association with Dr. George H. Evans, founded Alum Rock Sanatorium at San José in 1922. His active association with this institution continued to the time of his death.

He has been a member of many societies, and has been appointed on numerous medical committees of national importance. Among these are: Physician's Committee for the Improvement of Medical Care; Committee on Cost of Medical Care; the Interdepartmental Committee to Coordinate Health and Welfare Activities. He was a member of the California State Medical Society; a Fellow of the American Medical Association; a member of the California Academy of Medicine; the Association of American Physicians; American Association of Industrial Physicians and Surgeons; the American Public Health Association; the National Tuberculosis Association (of which he was Vice-President in 1920–1921); the American Trudeau Society; and the Laennec Society of Northern California. Among his outside activities he participated in founding the San Francisco Boys' Club of which he served as one of the first directors. He was a very active member in the Commonwealth Club of California. As a hereditary right, he was a member of the Society of Colonial Wars and the Society of American Wars. In 1918 he acted as Advisor to the Department of Intelligence and Research of the American Red Cross in Europe.

One of his foremost interests in latter years was in the controversial field of medical economics. The results of his many personal activities in various forms of medical practice, as well as his wide acquaintance among the Executives of National Foundations, together with his extensive collection of reprints and reports on this subject, gave him certain very positive opinions that did not always entirely agree with those formulated by the official representatives of organized medicine. Because of his inherent honesty and the stimulating vigor of his presentation, his views in this field were always respected, though at times heartily disagreed with, even by those who cherished deep personal affection.

Philip King Brown continued his extensive medical activities up to the very day of his last illness, and when faced with the knowledge of the necessity for a serious operation, knowing that it was an urgent matter, he approached this crisis as he had many others in the past—in the spirit of the true physician. Unfortunately he did not survive this ordeal.

One of the great pleasures of latter years was the knowledge that his son, Cabot, was carrying on the family tradition in medicine.

His loss is felt keenly throughout California and many parts of the United States. When he laid down the medical torch, he could have the satisfaction of knowing that his had been a life in the true spirit of Æsculapius.

HAROLD GUYON TRIMBLE.

AMERICAN TRUDEAU SOCIETY

Dr. John B. Barnwell, University Hospital, University of Michigan, Ann Arbor, is Chairman of the Committee on Nominations for officers and Council members of the American Trudeau Society. The other members are Dr. P. A. Yoder, Forsyth County Sanatorium, Winston-Salem, North Carolina, and Dr. Sidney J. Shipman, 490 Post Street, San Francisco, California.

The Committee asks members of the Society to send them nominations for President-elect, Vice-President and Secretary-Treasurer, as well as for five members of the Council, the latter to serve three years.

The Committee will submit its report at the Business Session on May 5, 1941, to be held at the Hotel Gunter, San Antonio, Texas.

BCG VACCINATION IN MONTREAL[1]

Statistical Analysis of the Results of Research by Dr. J. A. Baudouin on BCG Vaccination in Montreal

J. W. HOPKINS[2]

INTRODUCTION

It is now nineteen years since Calmette announced the production of an attenuated strain of tubercle bacilli, named BCG, which, while maintaining unimpaired its original antigenic properties, had definitely lost all virulence, as judged by the ability to create active tuberculous lesions transmissible by infection, and sixteen years since the large-scale vaccination of children with BCG was begun in France. These developments naturally aroused wide-spread attention, and in the intervening years laboratory workers and physicians in many countries have labored to investigate the bacteriological, immunological, veterinary and medical properties of Calmette's organism.

At the present time it seems fair to say that in spite of the well known views of Petroff and some others, and of the renewed controversy temporarily generated by the Lübeck disaster, the prevailing opinion is that BCG is completely innocuous and produces no untoward effects in either animal or human subjects to whom it is administered as prescribed (5). Granting the innocuity of the preparation, however, there is no similar general agreement as to whether or not any positive benefit may be expected to accrue from its use. It is true that there are reported in the literature the results of vaccination experiments in several parts of the world in which the incidence of tuberculosis amongst those vaccinated was below that in the same age groups of the population at large, or alternatively, in specific control groups (3, 4). On the other hand, critics have put forward one or more of three main objections to any facile interpretation of these observations: (*1*) that the observed differences in mortality, *etc.* were statistically insignificant and hence might

[1] From the National Research Laboratories, Ottawa, Canada, read before the Canadian Tuberculosis Association, Montreal, June 24, 1940. Published as N. R. C. No. 986.

[2] Statistician, Division of Biology and Agriculture, National Research Laboratories, Ottawa.

well have been fortuitous; (*2*) that the vaccinated children were not a random sample representative of the same population as those taken as controls; or (*3*) even if statistically significant differences are observed in originally comparable groups, it may, nevertheless, be erroneous to conclude that these are due to the effect of BCG and not to differences in the subsequent medical or home care, frequency of inspection, *etc.* of the two groups. The original statistics published on various occasions by Calmette himself have been sharply criticized on all these grounds (1, 2). Later workers have for the most part concentrated their attention on those sections of the population exposed to determinate contact with active agents of infection, as in these classes a much higher rate of mortality prevails, and any marked effect of vaccination should be demonstrable in groups numbered in the hundreds rather than in the tens of thousands (2). Here again, however, the objections previously mentioned may be put forward, with a varying degree of plausibility in each case (3). Space will not be taken to expand further upon these points, but it is necessary to mention them, as it is in the light of such facts that the results of Doctor Baudouin's studies of BCG vaccination in Montreal, now to be described, must be considered.

HISTORY OF DOCTOR BAUDOUIN'S RESEARCH

In 1925 an Associate Committee on Tuberculosis was formed by the National Research Council of Canada to arrange and supervise research on tuberculosis in man and animals. In 1926, with the assistance of grants from this Committee, Doctor Baudouin undertook the investigation of the efficacy of BCG as a vaccine for children. From June, 1926 to December, 1938, over 20,000 Montreal infants were vaccinated on the advice of the physicians attending at birth and with the consent of the parents. These were for the most part drawn from the lower middle class or poorer sections of the community. The vaccine was in all cases administered orally.

A record of the identity of all infants vaccinated has been maintained by Doctor Baudouin, but the systematic collection of further information has been limited largely to 793 of these vaccinated children, for whom there was evidence of contact with a positive sputum case of tuberculosis, and to approximately 1,200 unvaccinated children in similar contact, taken as controls. Even so, the number of cases under observation was such that the four public health nurses employed on this project found it possible to visit each child only once a year. On the

occasion of these visits, records were made in the form recommended by the Health Organization of the League of Nations. No distinction was made between vaccinated and controls in respect of frequency of visits.

During the earlier years of the investigation, the Bruchési and Royal Edward Institutes of Montreal chose as controls unvaccinated children who were in contact with contagious cases of tuberculosis and who were believed to be living under environmental conditions similar to those of the vaccinated. More recently, however, in the effort to secure maximum comparability, the controls have been derived from within the same families as the vaccinated, and it is accordingly possible to consider separately the statistics (*1*) for what Doctor Baudouin has termed the "special" group, consisting of vaccinated and control children living in the same families, and (*2*) those for what has been termed the "outside" group, comprising vaccinated and controls not in the same families.

In 1939, the Associate Committee on Medical Research of the National Research Council named a panel to make an independent report on Doctor Baudouin's research, including a statistical analysis of the data. The panel consisted of Mr. F. E. Lathe of the National Research Laboratories, Chairman; Dr. N. E. Gibbons, Bacteriologist, and Dr. C. B. Stewart, M.D., then secretary of the Associate Committee on Medical Research, also of the National Research Laboratories; Dr. G. J. Wherrett, of the Canadian Tuberculosis Association, and the writer.

STUDY OF RECORDS BY PANEL

The panel made an independent study of each individual case record as of December 31, 1938. This involved the examination by Doctor Stewart of 671 family histories, and the tabulation, on forms designed to facilitate subsequent statistical analysis, of the complete records of some 1,950 vaccinated and control children. In order to appraise the statistical comparability of the two groups of vaccinated and controls, a careful scrutiny was made by Doctors Stewart and Wherrett of the medical details relevant to proof of contact, and to the individual diagnoses of mortality and morbidity and the extent to which these were confirmed by autopsy, X-ray observation, *etc.* It will be appreciated that this could not have been accomplished without the cooperation of Doctor Baudouin and his staff, which was forthcoming unreservedly at all times. The decisions reached in each case were, however, those of the panel.

In order to avoid cases of congenital debility, all infants dying at less than one month of age were excluded from the tabulations. The panel also became convinced that it was necessary to exclude from the statistics the records of a total of 346 children for whom the evidence of effective contact with a positive sputum case of tuberculosis was judged to be inadequate for purposes of scientific record. A small number of diagnoses, particularly of tuberculosis morbidity, were likewise considered to be inadequately verified. On the other hand, it was decided to include in the analysis the records of 54 vaccinated and control children removed from a tuberculous environment to a foster home under the Grancher system. The contact of these was considered to be essentially the same as that of other children exposed to a contagious patient who was subsequently removed from the home or cured.

The remaining records are divisible into two classes: (*a*) those of children in contact with a case of pulmonary tuberculosis proven to be sputum-positive, or with a person who died of proven pulmonary tuberculosis without a sputum test, the assumption here being that such a patient was sputum-positive for two years before death; and (*b*) those of children in contact with a case of pulmonary tuberculosis proven only by X-ray examination, provided that *all* the children in the family had a positive tuberculin reaction. The former have been designated as "proven" and the latter as "presumptive" contacts. No case has been included in which the total duration of contact was less than one month.

It is now necessary to consider some statistical characteristics of these populations.

Age distribution: When tabulated according to the year of birth, an appreciable divergence of the age composition of the vaccinated and control children is apparent in both the "special" and "outside" groups. In the "special" group (vaccinated and controls in the same families), 55 per cent of the controls were born before December 31, 1930, whereas this period comprised only 23 per cent of the vaccinated births. Of the "outside" group (vaccinated and controls from different families), 57 per cent of the controls were born before December 31, 1929, as compared to 43 per cent of the vaccinated. The discrepancy in the "special" group is a natural consequence of the fact that the children taken as controls are in the great majority of cases the elder brothers and sisters of the vaccinated infants. In the "outside" group it arises from the fact, already mentioned, that the selection of controls by the Bruchési and Royal Edward Institutes was discontinued in the later years. In

both cases, however, the result is that total mortality or morbidity rates calculated from the entire vaccinated and control populations, respectively, are not directly comparable, because (*1*) the aggregate exposure of the controls to general risk has obviously been greater, and (*2*) the average age at beginning of contact with a positive-sputum case is not the same for the two groups. The first of these factors operates in favor of the vaccinated; the second, in favor of the controls.

In the absence of disturbances in the rate of mortality from causes other than tuberculosis from year to year, the first of these sources of bias may be overcome by making all comparisons between vaccinated and controls relate to corresponding age groups, although even this procedure would be invalidated by one or more years of abnormal mortality. This last consideration will be particularly important in view of the differences in birth dates outlined above. There do not, however, seem to have been any such pronounced fluctuations in child mortality during the period under review. In this connection the records of the Montreal Board of Health for the years 1926 to 1938 were consulted, and these indicated that the percentage of infant mortality due to infectious diseases had not shown any marked variation during this period. A tabulation of the causes of all deaths in Doctor Baudouin's population indicated that the total number attributable to contagious diseases was small and was not distributed in such a way as to suggest a concentration in any particular years. Finally, a tabulation was made of the total mortality rate (average of both vaccinated and controls) during the calendar year of birth and the succeeding calendar year, for each year from 1927 to 1937. These rates show considerable fluctuation, but not more than would be expected in view of the small size of the annual population. It may be inferred, therefore, that the statistics of mortality by age groups will not be seriously distorted by abnormalities of this kind, in merging the statistics for all children of corresponding age groups, irrespective of the actual calendar year to which their experience relates.

These age groups are, however, still unbalanced in respect to tuberculosis contact. Thus, in the "special" group, 61 per cent of the control children were not exposed to any known contact with a positive-sputum case during the calendar year of their birth, whereas only 26 per cent of the vaccinated children enjoyed this immunity. Similarly, during the calendar year subsequent to that of birth, 47 per cent of the controls as compared to only 30 per cent of the vaccinated children were not, as

far as is known, exposed to any effective contact. It is clear that, in these circumstances, mortality and morbidity rates must be computed after excluding from the younger age groups all children prior to contact.

The nature of contact of the vaccinated and control children has also been recorded, according to whether contact was with parent, brother or sister, other patient or with more than one infective individual. The high proportion (30 to 40 per cent) of sustained contacts with persons other than immediate relatives is a noteworthy feature that is, however, common to all four groups. Although the "outside" children had relatively more contacts with a tuberculous father or mother only and include a smaller proportion of individuals with more than one contact, the nature of contact of the vaccinated and controls on the whole shows a satisfactory degree of similarity. It was not possible to classify these contacts on the basis of bacillary intensity.

Mortality from causes other than tuberculosis: After restriction and adjustment of the vaccinated and control populations for the reasons outlined, the numbers available are insufficient to establish reliable mortality rates for the individual years of life. Useful comparisons may, however, be made between the aggregates of the rates for the first five age groups of each class of children, as in this way the populations and the differences involved are increased to a point at which some statistical discrimination is possible This aggregate of rates of mortality from causes other than tuberculosis is identical in the "special" vaccinated and control groups at 69 per 1,000. The aggregate of the first five rates observed in the "outside" vaccinated, at 49 per 1,000, is somewhat lower, but the difference between this and the foregoing value of 69 does not significantly exceed its standard error. (The standard error is the commonly adopted statistical measure of random sampling variation. A range of twice the standard error may be expected to comprise 95 per cent of the fluctuations occurring in successive random samples from the same population.) In this important respect, therefore, the "outside" vaccinated, the "special" vaccinated and the "special" controls may be said to exhibit a reasonable degree of homogeneity. On the other hand, the "outside" controls have an aggregate of mortality rates for the first five age groups of 120 ± 26, as compared with 69 per 1,000 for the "special" controls and 49 for the "outside" vaccinated. It is clear, therefore, that the mortality experience of the "outside" controls, even from causes other than tuberculosis, cannot be regarded as equivalent to that of any of the other three groups of children. For this reason, the tu-

berculosis mortality or morbidity rates of the "outside" controls can likewise hardly be considered to be directly comparable with those of the other groups. The attempt to secure "outside" control children similar in all respects to the vaccinated must accordingly be regarded as not entirely successful; and it would, therefore, seem to be necessary to exclude the data for this group from further comparisons. The "outside" vaccinated, however, were not only selected, as already noted, in the same way as the "special" vaccinated children, but also show a reasonable degree of similarity to them in respect of nature of contact, duration of contact, general mortality and mortality from causes other than tuberculosis. It was, therefore, considered justifiable to combine the data for these two groups in order to provide a larger vaccinated population for comparison with the "special" controls. The following tables give the results of this procedure.

COMPARISON OF COMBINED POPULATION OF "OUTSIDE" AND "SPECIAL" VACCINATED CHILDREN WITH "SPECIAL" CONTROLS

Nature and duration of contact: The population and average duration of contact of the combined vaccinated and "special" control children in the various age classes are contrasted in tables 1a and 1b. In the majority of the age groups in both tables, the average contact during the current year is greater in the controls than in the vaccinated children. On the other hand, for the first five age groups the average accumulated contact does not differ appreciably in table 1a and actually operates in favor of the controls in the restricted population of table 1b. The explanation of this apparent anomaly is to be found in the fact that the second, third, fourth and fifth age groups of controls each show an increase in numbers over the preceding group, owing to the inclusion of children who came into contact with a tuberculous patient for the first time at these ages. Once these children were exposed, their average annual duration of contact was greater than that of the vaccinated; but for the first few years at least, their accumulated total falls below that of the vaccinated, who were for the most part in contact from birth. On the whole these two opposing tendencies are approximately balanced in the first five age groups. In the subsequent groups, however, the duration of contact, both current and total, becomes increasingly unfavorable to the controls, thereby progressively impairing their comparability with the vaccinated children of the same ages.

Tables 2a and 2b show the nature of contact of the two populations.

TABLE 1a

Population and average duration of contact of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED			CONTROLS		
	Population	Average duration of contact (months)		Population	Average duration of contact (months)	
		Current year	Total		Current year	Total
0	428	4.7	4.7	280	4.9	4.9
1	490	6.8	10.7	399	6.6	10.0
2	468	5.5	16.0	449	6.3	15.1
3	423	4.6	20.3	497	6.0	19.4
4	354	3.2	22.9	529	6.1	23.9
5	274	3.2	26.1	530	5.5	28.3
6	209	3.1	29.1	506	5.2	32.3
7	178	2.5	31.6	438	4.7	36.1
8	152	1.7	33.0	354	4.8	39.9
9	91	1.5	36.3	280	4.4	43.0
10	61	0.8	30.2	211	3.9	47.6
11	35	0.0	13.5	118	3.7	51.5
12	5	0.0	13.4	40	3.8	56.8

TABLE 1b

Population and average duration of contact of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED			CONTROLS		
	Population	Average duration of contact (months)		Population	Average duration of contact (months)	
		Current year	Total		Current year	Total
0	326	4.4	4.4	208	4.5	4.5
1	380	6.0	9.7	301	5.6	8.7
2	368	4.9	14.4	344	5.4	12.9
3	328	3.8	18.2	382	5.1	16.6
4	283	2.4	19.9	403	5.2	20.8
5	220	2.4	22.6	400	4.4	24.5
6	167	2.3	26.1	375	4.2	27.7
7	147	1.9	28.0	318	3.5	30.3
8	126	1.4	29.7	258	3.7	34.7
9	79	1.3	33.2	197	3.2	36.1
10	55	0.7	28.2	146	2.9	40.4
11	31	0.0	11.9	80	2.6	43.7
12	5	0.0	13.4	25	3.1	43.8

The similarity of the vaccinated and controls in this respect may be said to be quite satisfactory.

Confirmation of diagnoses: The following comments may be made respecting the diagnoses on which the mortality and morbidity rates now to be presented are based. In this connection, records were obtained from the Montreal Department of Health, from the hospitals where the deaths occurred or from the attending physicians.

TABLE 2a

Nature of contact of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases

CONTACT WITH:	VACCINATED		CONTROLS	
	Number	Per cent	Number	Per cent
Father or mother	282	47.4	325	45.0
Brother or sister	49	8.2	70	9.7
Other patient	212	35.6	231	32.0
More than one contact	52	8.7	96	13.3
Total	595		722	

TABLE 2b

Nature of contact of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases

CONTACT WITH:	VACCINATED		CONTROLS	
	Number	Per cent	Number	Per cent
Father or mother	208	45.0	233	43.6
Brother or sister	20	4.3	31	5.8
Other patient	190	41.1	199	37.2
More than one contact	44	9.5	72	13.5
Total	462		535	

Of 30 deaths from causes other than tuberculosis among the vaccinated children, 4 diagnoses were confirmed by autopsy and 11 by clinical and laboratory examinations at various Montreal hospitals. Full information concerning the family physicians was not recorded, but in at least 2 cases in which tuberculosis might have been suspected, the examinations were made by specialists in tuberculosis. There were 37 deaths from nontuberculous causes in the control group. Two of these were confirmed by autopsy, 15 by hospital examination and at least one other by a tuberculosis specialist.

A total of 8 deaths from tuberculosis occurred in the vaccinated group. Three of these were confirmed by autopsy, 3 others by hospital examination and one other by a specialist in tuberculosis. In the remaining case, diagnosed clinically as pulmonary and meningeal tuberculosis, both parents, with whom the child was in contact, had active pulmonary tuberculosis. Twenty-three tuberculosis deaths were recorded in the control group. One of these was confirmed by autopsy, and 10 were confirmed by hospital examination and at least 3 others by specialists in tuberculosis.

In classifying the cases of tuberculosis morbidity, four categories have been recognized: (*1*) active, consisting of those cases in which there was definite clinical, laboratory or radiographic evidence of an active tuberculous process; (*2*) latent, consisting of cases in which there was definite radiographic evidence of nonactive or healed lesions of pulmonary tuberculosis; (*3*) suspected tuberculosis, consisting of a small number of cases in which the evidence, although strongly suggestive, was considered insufficient to prove incontestably the diagnosis; and (*4*) doubtful, consisting of those cases listed as tuberculosis on what was considered to be evidence open to some question, for example, most cases diagnosed clinically as pulmonary tuberculosis, but not examined by X-ray.

Of the 37 active and latent morbid cases remaining in the vaccinated group after exclusion of 7 which were classified as doubtful or suspected only, 32 diagnoses were confirmed by radiographic or fluoroscopic examination and 32 by hospital examination. Clinical evidence alone was considered conclusive in one case diagnosed as pulmonary tuberculosis which developed after acute pleurisy and in 3 cases diagnosed as tuberculous adenitis in which the condition had persisted for two or three years. There were 81 active or latent cases of morbidity in the control group, of which 71 were confirmed by radiographic or fluoroscopic examination and 77 by hospital examination. No case diagnosed by clinical means alone was included in the active or latent groups.

General mortality: General mortality is shown by age groups in tables 3a and 3b. With but two exceptions in table 3a and two in 3b, the differences in rate per thousand are all in favor of the vaccinated. The numbers of children in the individual age groups are, however, too small to make these observations statistically significant. Even the combined rate for the first five age groups of controls in table 3a, at 126, differs from the vaccinated rate of 86 by only 1.8 times its standard error.

TABLE 3a

General mortality, by age groups, of combined population of "special" and "outside" vaccinated and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	428	8	19		280	9	25	
1	490	15	35		399	20	50	
2	468	7	15	86	449	13	29	126
3	423	4	9		497	8	16	
4	354	3	8		529	3	6	
5	274	1	4		530	1	2	
6	209	0	0		506	5	10	
7	178	0	0		438	0	0	
8	152	0	0		354	1	3	
9	91	0	0		280	0	0	
10	61	0	0		211	2	9	
11	35	0	0		118	0	0	
12	5	0	0		40	0	0	

TABLE 3b

General mortality, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	326	7	21		208	5	24	
1	380	14	37		301	15	50	
2	368	6	16	94	344	13	38	138
3	328	4	12		382	8	21	
4	283	2	8		403	2	5	
5	220	1	5		400	1	2	
6	167	0	0		375	3	8	
7	147	0	0		318	0	0	
8	126	0	0		258	1	4	
9	79	0	0		197	0	0	
10	55	0	0		146	2	14	
11	31	0	0		80	0	0	
12	5	0	0		25	0	0	

The corresponding rates for table 3b are 94 for the vaccinated and 138 for the controls; the apparent difference of 44 per thousand is 1.6 times its standard error. Both differences are suggestive but, as they stand,

not particularly strong statistically. The reason for this becomes clear when the general mortality is subdivided into its tuberculous and non-tuberculous components, as in tables 4 and 5.

TABLE 4a

Mortality from causes other than tuberculosis, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	428	6	14		280	4	14	
1	490	13	27		399	12	30	
2	468	6	13	64	449	9	20	72
3	423	3	7		497	3	6	
4	354	1	3		529	1	2	
5	274	1	4		530	1	2	
6	209	0	0		506	4	8	
7	178	0	0		438	0	0	
8	152	0	0		354	1	3	
9	91	0	0		280	0	0	
10	61	0	0		211	2	9	
11	35	0	0		118	0	0	
12	5	0	0		40	0	0	

TABLE 4b

Mortality from causes other than tuberculosis, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all cases prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	326	6	18		208	2	10	
1	380	13	34		301	8	27	
2	368	6	16	81	344	9	26	71
3	328	3	9		382	3	8	
4	283	1	4		403	0	0	
5	220	1	5		400	1	2	
6	167	0	0		375	3	8	
7	147	0	0		318	0	0	
8	126	0	0		258	1	4	
9	79	0	0		197	0	0	
10	55	0	0		146	2	14	
11	31	0	0		80	0	0	
12	5	0	0		25	0	0	

Nontuberculous mortality: Tables 4a and 4b give the mortality, by age groups, from causes other than tuberculosis. The total of the rates for the first five age groups of table 4a is 64 for the vaccinated and 72 for

TABLE 5a

Tuberculosis mortality, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	428	2	5		280	3	11	
1	490	2	4		399	8	20	
2	468	1	2	19	449	4	9	54
3	423	1	2		497	5	10	
4	354	2	6		529	2	4	
5	274	0	0		530	0	0	
6	209	0	0		506	1	2	
7	178	0	0		438	0	0	
8	152	0	0		354	0	0	
9	91	0	0		280	0	0	
10	61	0	0		211	0	0	
11	35	0	0		118	0	0	
12	5	0	0		40	0	0	

TABLE 5b

Tuberculosis mortality, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED				CONTROLS			
	Population	Number deaths	Rate per 1,000		Population	Number deaths	Rate per 1,000	
0	326	1	3		208	3	14	
1	380	2	5		301	7	23	
2	368	1	3	21	344	4	12	67
3	328	1	3		382	5	13	
4	283	2	7		403	2	5	
5	220	0	0		400	0	0	
6	167	0	0		375	0	0	
7	147	0	0		318	0	0	
8	126	0	0		258	0	0	
9	79	0	0		197	0	0	
10	55	0	0		146	0	0	
11	31	0	0		80	0	0	
12	5	0	0		25	0	0	

the controls, the difference being less than half its standard error. In the same way, table 4b gives a total rate of 81 for the first five age groups of vaccinated and 71 for the controls, the difference again being about half its standard error and thus without statistical significance. The aggregate mortality of the first five age groups from causes other than tuberculosis may, therefore, be considered to be essentially identical in the vaccinated and control children, a circumstance which provides some further justification for the combination of the "special" and "outside" vaccinated groups for comparison with the "special" controls.

Mortality from tuberculosis: Mortality from tuberculosis is shown in tables 5a and 5b. Including contacts with both proven and presumptive positive-sputum cases (table 5a), the sum of the death rates for the first five vaccinated age groups is 19, and for the controls 54. The difference of 35 per thousand is 2.6 times its standard error of 13.6. When only contacts with proven positive-sputum cases are considered (table 5b), the corresponding rates are 21 for the vaccinated and 67 for the controls, the difference of 46 per thousand being 2.7 times its standard error. It may be inferred, therefore, that the inconclusive statistical difference between the general mortality of the vaccinated and control populations (table 3) was due to their similarity in respect of nontuberculous death rates, which comprised the major part of the total observed mortality and thus served to mask real differences in deaths from tuberculosis, in both the entire and restricted populations. The individual age groups are still too small to permit the determination of reliable rates for specific years. This will be appreciated when it is noted that the largest vaccinated age group in table 5a contains only 490 children, among whom 2 deaths from tuberculosis are recorded. In fact in the whole population there were but 8 deaths from tuberculosis in the vaccinated, distributed between five age groups, and 23 in the controls, distributed between six groups.

Tuberculous infection: There were, of course, appreciably more cases of tuberculosis morbidity than of mortality, and the statistics of these are set forth in tables 6a and 6b. The populations of table 6a give an aggregate active morbidity rate for the first five age groups of 31 per thousand for the vaccinated and 120 for the controls. The difference of 89 between these is 4.9 times its standard error, and hence may be regarded as statistically quite significant. Addition of the latent cases results in a five-year rate of 111 for the vaccinated and 196 for the controls, the difference of 85 per thousand being 3.4 times its standard error;

TABLE 6a

Tuberculosis morbidity, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1-DEC. 31) AFTER BIRTH	VACCINATED											CONTROLS								
	Population	Active		+Latent			+Suspected Tuberculosis			+Doubtful			Population	Active		+Latent			+Suspected Tuberculosis			+Doubtful		
		Number	Rate	Number	Rate		Number	Rate		Number	Rate			Number	Rate	Number	Rate		Number	Rate		Number	Rate	
0	428	0	0	1	2		1	2		2	5		280	2	7	2	7		2	7		5	18	
1	490	5	10	9	18		9	18		10	20		399	5	13	7	18		7	18		10	25	
2	468	4	9	31	12	26	111	12	26	118	13	28	138	449	11	24	120	14	31	196	15	33	202	17	38	230
3	423	4	9		13	31		15	35		17	40		497	21	42		33	66		34	68		35	70	
4	354	1	3		12	34		13	37		16	45		529	18	34		39	74		40	76		42	79	
5	274	5	18		15	55		15	55		18	66		530	19	36		47	89		49	92		51	96	
6	209	4	19		12	57		12	57		16	77		506	15	30		50	99		51	101		54	107	
7	178	1	6		11	62		11	62		15	84		438	12	27		45	103		46	105		47	107	
8	152	2	13		11	72		11	72		15	99		354	11	31		41	116		42	119		43	121	
9	91	1	11		4	44		4	44		5	55		280	11	39		34	121		35	125		36	129	
10	61	0	0		3	49		3	49		4	66		211	4	19		24	114		25	118		25	118	
11	35	0	0		2	57		2	57		2	57		118	2	17		16	136		16	136		16	136	
12	5	0	0		0	0		0	0		0	0		40	1	25		6	150		6	150		6	150	

TABLE 6b

Tuberculosis morbidity, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1–DEC. 31) AFTER BIRTH	VACCINATED										CONTROLS									
	Population	Active		+Latent		+Suspected Tuberculosis		+Doubtful			Population	Active		+Latent		+Suspected Tuberculosis		+Doubtful		
		Number	Rate	Number	Rate	Number	Rate	Number	Rate			Number	Rate	Number	Rate	Number	Rate	Number	Rate	
0	326	0	0	1	3	1	3	1	3		208	1	5	1	5	1	5	4	19	
1	380	5	13	8	21	8	21	8	21		301	5	17	5	17	5	17	8	27	
2	368	4	11	33	9	24	100	9	24	110	9	24	120	344	11	32	146	12	35	210	13	38	218	15	44	255
3	328	3	9	9	27	11	34	12	37		382	20	52	29	76	30	79	31	81	
4	283	0	0	7	25	8	28	10	35		403	16	40	31	77	32	79	34	84	
5	220	4	18	10	45	10	45	12	55		400	18	45	36	90	37	93	39	93	
6	167	3	18	7	42	7	42	10	60		375	15	40	38	101	38	101	41	109	
7	147	1	7	9	61	9	61	12	82		318	11	35	33	104	34	107	35	110	
8	126	2	16	10	79	10	79	13	103		258	11	43	31	120	32	124	33	128	
9	79	1	13	4	51	4	51	5	63		197	10	51	28	142	29	147	30	152	
10	55	0	0	2	36	2	36	3	55		146	4	27	20	137	21	144	21	144	
11	31	0	0	1	32	1	32	1	32		80	2	25	12	150	12	150	12	150	
12	5	0	0	0	0	0	0	0	0		25	1	40	5	200	5	200	5	200	

while the inclusion of active, latent and suspected cases increases the vaccinated rate to 118 and that for the controls to 202, the difference of 84 being in this case 3.0 times its standard error. Inclusion of the doubtful cases does not appreciably modify the comparison. Similar, but even more pronounced differences are to be noted in table 6b, which includes only the results for those children in contact with proven positive-sputum cases. The sum of the first five yearly rates of active tuberculosis morbidity is 33 per thousand for the vaccinated and 146 for the controls, or a difference of 113 in favor of the vaccinated, which is 5.1 times its standard error. For active plus latent cases, the rates are 100 and 210, the difference of 110 per thousand being 3.8 times its standard error; while the further addition of the suspected cases of tuberculosis morbidity (few in actual numbers) increases these figures to 110 and 218, and results in a difference of 108 per thousand, 3.6 times its standard error.

The morbidity figures thus exhibit striking differences in favor of the vaccinated children. These differences are accentuated when the statistics for morbidity of the active type are combined with those for mortality to yield rates of what has been termed "total tuberculosis pathological infection," as in tables 7a and 7b. When this is done, the differences between the vaccinated and controls in respect of number of pathological cases are increased to a level at which it is possible to make statistical comparisons between certain of the individual age groups. The observed differences throughout both tables are consistently in favor of the vaccinated. In table 7a, including contact with both proven and presumptive positive-sputum cases, they attain the level of statistical significance (twice the standard error) for the third, fourth, fifth and eighth groups and fall barely short of the required margin in the second. In table 7b, which is confined to contacts with proven positive-sputum cases, the pathological rate for the controls is significantly above that of the vaccinated in the third, fourth and fifth age groups and is just short of a significant excess in the first and sixth.

The indications are, therefore, that, under the conditions of this investigation, the oral administration of BCG vaccine at birth substantially reduced the incidence of tuberculosis during the third, fourth and fifth years of life, and that, had larger numbers been available for comparison, significant reductions would probably also have been demonstrable in the first two years. It is true that even after the exclusion of a variety of unsatisfactory elements from the statistical populations,

TABLE 7a

Total tuberculosis pathological infection, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including contacts with both proven and presumptive positive sputum cases, but excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1-DEC. 31) AFTER BIRTH	VACCINATED			CONTROLS			DIFFERENCE BETWEEN CONTROL AND VACCINATED, RATE PER 1,000
	Population	Number cases	Rate per 1,000	Population	Number cases	Rate per 1,000	
0	428	2	5	280	5	18	13 ± 8.6
1	490	7	14	399	13	33	19 ± 10.4
2	468	5	11	449	15	33	22 ± 10.7*
3	423	5	12	497	26	52	40 ± 10.8*
4	354	3	8	529	20	38	30 ± 9.6*
5	274	5	18	530	19	36	18 ± 11.4
6	209	4	19	506	16	32	13 ± 12.2
7	178	1	6	438	12	27	21 ± 9.7*
8	152	2	13	354	11	31	18 ± 13.0
9	91	1	11	280	11	39	28 ± 15.9
10	61	0	0	211	4	19	—
11	35	0	0	118	2	17	—
12	5	0	0	40	1	25	—

* Indicates difference greater than twice its standard error.

TABLE 7b

Total tuberculosis pathological infection, by age groups, of combined population of "special" and "outside" vaccinated, and of "special" control children, including only contacts with proven positive sputum cases, and excluding all children prior to calendar year of first contact

CALENDAR YEARS (JAN. 1-DEC. 31) AFTER BIRTH	VACCINATED			CONTROLS			DIFFERENCE BETWEEN CONTROL AND VACCINATED, RATE PER 1,000
	Population	Number cases	Rate per 1,000	Population	Number cases	Rate per 1,000	
0	326	1	3	208	4	19	16 ± 9.9
1	380	7	18	301	12	40	22 ± 13.2
2	368	5	14	344	23	67	53 ± 15.0*
3	328	4	12	382	25	65	53 ± 14.0*
4	283	2	7	403	18	45	38 ± 11.5*
5	220	4	18	400	18	45	27 ± 13.7
6	167	3	18	375	15	40	22 ± 14.4
7	147	1	7	318	11	29	22 ± 11.6
8	126	2	16	258	11	43	27 ± 16.9
9	79	1	13	197	10	51	28 ± 20.2
10	55	0	0	146	4	27	—
11	31	0	0	80	2	25	—
12	5	0	0	25	1	40	—

* Indicates difference greater than twice its standard error.

as already described, these can still hardly be said to have had an identical exposure to infection. In the first five age groups, however, the vaccinated, which show in some cases a slightly higher accumulated duration of contact and were clearly of a lower average age at the beginning of contact, may plausibly be said to have been, on the whole, at a disadvantage in comparison with the controls. It therefore seems reasonable to ascribe the observed differences in the "pathological infection" of these groups to the effects of vaccination. On the other hand, the similarity of these vaccinated and control groups in respect to non-tuberculosis mortality is not indicative of any pronounced paraspecific immunity resulting from BCG, as has been suggested by some investigators. Beyond these five groups it is clearly unwise to go, in view of the pronounced differential exposure, adverse to the controls at the higher ages. For this reason the apparent difference between the eighth age groups in table 7a must be regarded as subject to considerable uncertainty. In the opinion of the panel the only way in which acceptable information respecting the duration of the effectiveness of vaccination may be secured is by continued observation of the children now in the lower age classes.

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PULMONARY TUBERCULOSIS IN MEDICAL STUDENTS AND NURSES[1,2]

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PULMONARY TUBERCULOSIS IN MEDICAL AND NURSING STUDENTS

The occurrence of pulmonary tuberculosis in nurses and medical students has been the subject of numerous reports and investigations. These have been reviewed recently by Soper and Amberson (1). The present communication is a report of the results of tuberculosis case-finding applied to groups of medical and nursing students at the Cornell University Medical College and the New York Hospital.

The methods employed were the intracutaneous tuberculin test and the roentgenogram of the chest. The tuberculin tests were made with a commercial Old Tuberculin of uniform potency and one and one-half times stronger than that of the International Standard. The first dose was 0.01 and the second, 1.0 mg. The latter was given if the first elicited no reaction. The reactions were read two days after the intracutaneous injections. The reactions were considered positive if the skin was raised over an area of a diameter of 5 mm. or more. The roentgenograms of the chest were made in the X-ray Department of the Hospital with standard technique, single posteroanterior views being used.

Tuberculin tests: Tests were made on first-year medical students and student nurses within two months of admission to their respective schools and during the last month of their final year. In addition a few student nurses were tested during their second year.

Medical students: Six first-year classes were tested. The percentage of positive reactors varied from 75 to 89. Collectively, of the 315 first-year students tested, 259, or 82.2 per cent, were positive and 56, or 17.7 per cent, were negative.

Three fourth-year classes, graduating in 1935, 1936 and 1937 were similarly examined. Nearly all of the students in these classes were

[1] From the New York Hospital and Departments of Medicine and Pathology, Cornell University Medical College, New York City.

[2] This study was aided by a grant from the International Health Division of the Rockefeller Foundation.

tested. Of the total of 147 tested, 135, or 91.8 per cent, were found positive and 12, or 8.1 per cent, were negative. The percentage of positive reactors in the fourth-year classes tested was thus 9.6 percentage points higher than in the first-year classes.

Student nurses: Most of the members of the classes of 1935 to 1941, inclusive, were tested in their first year. Of the total of 278 first-year students tested, 216, or 77.6 per cent, were positive and 62, or 22.3 per cent, were negative. The classes of 1934 and 1936 were examined during their second year. The class of 1936 had been considerably enlarged by transfer of students from another training school. Of the total of 69 second-year students tested, 57, or 82.6 per cent, were positive and 12, or 17.4 per cent, were negative. Five classes, those of 1933, 1935, 1936, 1937 and 1938, were examined at the end of their third year. Of the total of 130 graduating students tested, 119, or 91.5 per cent, were positive and 11, or 8.5 per cent, were negative. The student nurses thus showed an increase of positive reactors from 77.6 per cent of the first-year students tested to 91.5 per cent of the graduating students tested.

Because of the absence of any demonstrated practical necessity for retesting previously positive reactors, the original plan of retesting all students in their final year was discontinued after 1937. All negative reactors, however, have been retested before graduation. In all classes there has been a gradual decline in the number remaining tuberculin-negative in successive years of the training period. The percentage of negative reactors shortly before graduation in both the medical and nursing student groups has varied in different years from zero to 14.3 per cent. The average for the nursing students (of the classes of 1933 to 1939 inclusive) has been 6 per cent negative on graduation and for the medical students, 8.7 per cent.

Chest Roentgenography

Medical students: The medical students have had yearly roentgenograms of the chest since 1934. The first-year classes have been subjected to the procedure at the beginning of the academic year. Although the attempt has been made to have the entire class roentgenographed within a month of entrance, in some years this has not been completed until the end of the second month after entrance. The second and third-year classes, including students who have transferred from other medical schools, have been roentgenographed at the beginning of the second and

toward the end of the third year, respectively. The fourth-year classes have been roentgenographed as near the end of the academic year as practicable and always within two months of graduation.

The following data pertain to the six classes (1934 to 1939 inclusive) which have graduated since the program was initiated. The four latest classes were roentgenographed each year. The classes of 1934 and 1935 had begun the course before the institution of the routine and were not roentgenographed until their fourth and third years, respectively.

A total of 442 students each had at least one roentgenographic examination. Seventy-one, or 16.1 per cent, had calcified deposits in the tracheobronchial lymph nodes or in the pulmonary parenchyma, or in both. These were interpreted as healed lesions of the childhood-type. In 22, or 5.0 per cent, there were shadows at either or both of the extreme apices of only several millimetres thickness. These were interpreted as thickening of the apical pleura with possibly some parenchymal involvement. This group was classified as doubtful. The calcified shadows and the doubtful apical shadows were found in every instance in the student's initial roentgenogram. None appeared in subsequent roentgenograms of those whose original film had been entirely negative. There was also no instance in which these shadows changed during the period of observation and, incidentally, no student whose initial film revealed either type of shadow was in the group who later developed definite pulmonary infiltrations. Five, or 1.1 per cent, had shadows characteristic of chronic pulmonary tuberculosis in their initial roentgenogram. The lesions were all minimal in extent. Only 2 of the 5 were found in the first academic year. The other 3 belonged to the classes of 1934 and 1935 which were not roentgenographed until their fourth and third years, respectively. Four other students, or 0.9 per cent, who had been negative in their initial roentgenographic examination developed shadows characteristic of chronic pulmonary tuberculosis in subsequent years. Three were minimal and one was moderately advanced when found. None had complained of any symptoms before the lesion was discovered. In addition to having shown no roentgenographic evidence of tuberculosis, 3 of the 4 had originally been negative to 1.0 mg. of tuberculin. These 9 students, 2.0 per cent of the total, who were discovered to have chronic pulmonary tuberculosis, represent the entire number of cases found, including the apparently arrested as well as those in whom progressive disease was demonstrated. Four of the 9 had lesions which were obviously progressive and these were re-

ferred to sanatoria immediately after discovery of the disease. The other 5, for various reasons not under our control, were allowed to continue at work and complete their course. Of these, there are only 2 in regard to whom we possess subsequent information sufficient to determine whether their disease was arrested at the time of discovery. One of these has never had any symptoms or physical signs attributable to his lesion which has remained unchanged in serial roentgenograms over a period of four years. The other is known to have had progression of his disease since graduation. The 9 students were all between the ages of twenty and twenty-six. The average age of all of the students on entrance to medical school was twenty-two. Forty-five, or 10.2 per cent, of the 442 students studied were women and one of the 9 in whom chronic pulmonary tuberculosis was found was a woman.

For purposes of comparison with similar data which have been and may in the future be collected in other institutions, it is perhaps of interest to calculate the occurrence of new cases of pulmonary tuberculosis in the student body on a person-year basis. For this calculation, only that portion of the above data is applicable which relates to the development of lesions in the roentgenograms of the students who had more than one observation and in whom the original roentgenogram was negative. The corrected total is 1,152 person years of observation. The 4 new cases of pulmonary tuberculosis that occurred represent a rate of 0.35 per 100 per year.

Student nurses: The undergraduate student nurses in training at the New York Hospital have had yearly roentgenograms made of the chest since 1933. The first-year classes have been subjected to the routine shortly after admission of the students to the training school. The second-year classes have been roentgenographed toward the end of the year. The third-year, or graduating classes, have also been roentgenographed toward the end of the year, usually within one or two months of completion of the three-year course. The following data pertain to the seven classes (1933 to 1939 inclusive) which have graduated since the program was started. Of these classes, all but two were routinely roentgenographed each of the three undergraduate years. The class of 1933 was roentgenographed only once, in its graduating year, and the class of 1934 only twice, at the beginning of its second year and at the end of its third year.

The total number of student nurses roentgenographed was 269. Fifty-two, or 19.3 per cent, of these were found to have calcified nodules,

14, or 5.2 per cent, had doubtful apical shadows of not more than a few millimetres' thickness. These were, in each instance, present in the initial film. As was found to be the case also in the medical students, none of the persons whose roentgenograms showed calcified deposits or doubtful apical shadows later developed definite pulmonary infiltrations during the period of observation. Three nurses, or 1.1 per cent, of the entire group, were found to have definite pulmonary lesions of the so-called adult-type. They were all in the minimal stage when discovered. Two of the 3 were found in the initial roentgenogram. One only developed in a nurse whose initial film had been negative. Although one of the 2 in whom evidence of chronic pulmonary tuberculosis was found in the initial roentgenogram was a member of the class of 1934 and, therefore, did not receive this initial examination until her second year, we feel reasonably sure that her lesion was of long standing and did not develop after her entrance into the training school. She was over thirty years of age, considerably older than the average, had a family history of tuberculosis and her lesion with no treatment has remained unchanged for five and one-half years since its discovery. In view of this retrospective evidence that the disease was already in an arrested stage when found, we feel justified in the assumption that it had been present a year earlier when the nurse began her course of training. The second nurse who was discovered to have pulmonary tuberculosis had her first roentgenographic examination made within two months of her admission to the school and her lesion was discovered at that time. It is most likely, therefore, that her lesion was present prior to her admission. The one nurse who is known to have developed tuberculosis during her course of training had negative films in her first and second years. Her tuberculin test had been negative to 1.0 mg. OT in her first year. She had not been retested. Her lesion was discovered in the routine roentgenogram taken toward the end of her third year. Both of the latter two nurses were sent to a sanatorium promptly after discovery of their disease. Neither ever had symptoms and both returned to complete their courses successfully. They were both under twenty-five years of age. The average age of all of the student nurses studied was twenty-one years.

Excluding the two nurses who, the evidence indicates, had pulmonary tuberculosis on entering school, we thus have found only one who developed the disease during the three-year training period, a percentage of 0.37 per cent of the 269 student nurses studied. Although statistics

based on a single case are of little significance, it may be of some interest to calculate the rate on a person-year basis as was done above for the medical students. The corrected total is 545 person-years, in which occurred one new case of pulmonary tuberculosis, a rate of 0.18 per 100 per year.

Discussion

Although our observations have been on a relatively small number of students and further experience in tuberculosis case-finding may reveal conditions that we have not found during the period studied, it does, nevertheless, seem that a limited number of conclusions are justified. In comparing the incidence of pulmonary tuberculosis in these student groups and in similar age groups not so occupied, certain interesting differences and similarities are found. Thus, our student nurses, with a total incidence of 1.1 per cent and a yearly incidence of new lesions of only 0.18 per cent, do not appear to develop tuberculosis more frequently than women of the same age group applying for employment or employed in the Metropolitan Life Insurance Company where Fellows (2) reports an average incidence of 1.44 per cent with pulmonary tuberculosis in 24,000 female applicants of average age of twenty years observed over a ten-year period from 1927 to 1938. The rate of development of new lesions in female employees aged eighteen to twenty-two was reported by Fellows (3) to be 0.25 per hundred per year. In our student nurses, therefore, an occupational hazard has not manifested itself as roentgenographically recognizable disease during the period of training. The tuberculosis rate in the medical students, also, though slightly higher, does not appear to be significantly above the expected rate in their age group. The rates both in the nursing and in the medical students are certainly considerably below those reported in some other institutions of similar nature. This variation of tuberculosis rates in different hospitals and medical schools has been previously noted by Hetherington, McPhedran, Landis and Opie (4) and by Soper and Amberson (1). It undoubtedly depends on numerous factors only one of which is the opportunity for acquiring infection. The New York Hospital, unlike most voluntary hospitals in New York City, has since 1934 maintained a pulmonary ward service with nineteen beds occupied by patients with pulmonary tuberculosis. Both the medical and nursing students have periods of service on this ward as well as in an active pulmonary clinic. Patients with pulmonary tuberculosis are also treated in other depart-

ments of the hospital for other conditions or when thoracic surgery is necessary. The patients receive group isolation in the pulmonary ward and individual isolation in other wards if the sputum is positive for tubercle bacilli. Whether the relatively low incidence of pulmonary tuberculosis in the student groups is due entirely to these rather rigid precautions is problematical. That the students are not completely protected from new infections, whether acquired within or without the hospital, is evident from the increase in the number of positive tuberculin reactors in successive years. Other factors which we think may contribute to the satisfactorily low rate of development of new lesions, at least in reference to the nursing students, are the conditions of housing and of nutrition which we believe to be exceptionally good, and the age of the students who are somewhat older (of an average age of twenty-one on admission to the school) than in many other training schools. A high percentage of positive tuberculin reactors in our medical and nursing student groups on admission may indicate that most of them had a considerable degree of acquired resistance. The fact that four out of five, in the combined groups, who developed new pulmonary lesions were tuberculin-negative on beginning their course may be of significance in this regard, although the number is too small to justify any far-reaching conclusion. At least our experience would tend to support the observations of others that the students who are originally tuberculin-negative are more likely to develop clinically significant disease than those originally tuberculin-positive.

To establish more firmly the conclusion that there is no considerable occupational hazard for the medical and nursing students in this hospital, it will be necessary to obtain some data regarding the morbidity of the group in the years following graduation. These data have not yet been collected although plans are now being made for a continuous follow-up system by means of questionnaires which will be sent every few years to all graduates of the medical and nursing schools.

PULMONARY TUBERCULOSIS IN GRADUATE NURSES

A study of the frequency of pulmonary tuberculosis in the graduate nursing staff of the New York Hospital from September, 1932 to July, 1939 has been undertaken. Because of a rather large yearly turnover in the composition of the graduate nursing staff, it has been difficult to establish an efficient case-finding program, although, as our observations show, the need for such a program is, if anything, greater for this group

than for the student group. During the winter of 1932–33 a roentgenographic survey was made of all of the graduate nurses then employed in the hospital, and subsequently the nurses were requested to accept a routine roentgenogram of the chest within a few weeks after employment and at yearly intervals thereafter, but were not required to do so.

Tuberculin testing has not been carried out routinely but a larger group of graduate nurses was tested in April, 1933 and another smaller group in June, 1934. All together, 292 graduate nurses were tested, of whom 268, or 91.7 per cent, were positive and 24, or 8.2 per cent, were negative.

Chest Roentgenography

Survey of 1932–1933: The total number of nurses examined in the survey was 290. This number represents virtually all of the graduate nurses who were at that time employed on the hospital staff. The hospital had moved to its present location in the fall of 1932, and the survey was conducted during its first year in the new location. At that time many of the wards were not yet in operation and the nursing staff was consequently smaller than it is at present. One-hundred and ninety-nine films, or 68.6 per cent, were negative; 48, or 16.6 per cent, showed calcified pulmonary nodules, calcified tracheobronchial nodes or both, without other abnormal shadows. An additional 21, or 7.2 per cent, had such calcified deposits combined with doubtful or definite infiltrative lesions; 19, or 6.5 per cent, showed only doubtful shadows at the extreme apex of one or both lungs. No progression of the doubtful shadows was found in subsequent films when later examinations were made; 24, or 8.3 per cent, had definite pulmonary infiltrations characteristic of chronic pulmonary tuberculosis. In 17, or 70.8 per cent, of the 24, the disease was of minimal extent, and in 7, or 29.2 per cent, it was moderately advanced. There were no instances of far advanced disease. A history of symptoms which might have led to the discovery of the disease was obtainable in 5 of the 24 cases; 15 nurses had had no symptoms; in 3 instances the record was incomplete and 2 nurses had been treated for pulmonary tuberculosis. This emphasizes again the paucity of symptoms in persons who may have radiographically well defined and, in some instances, fairly extensive lesions.

Cases found subsequent to the 1932–1933 survey: During the following five and one-half years (1934–1939), the majority of the nurses employed in the hospital received at least one roentgenographic examination of the

chest. This procedure, as has been stated above, was not obligatory, and particularly among those who remained for only short periods, examination was sometimes omitted. Twenty-seven additional cases of pulmonary tuberculosis came to light during this period; the majority of them were found by routine roentgenograms, although several nurses had symptoms which led to the discovery of the disease.

Discussion

In the two groups of graduate nurses reported above, there was a total of 51 with definite roentgenographic evidence of chronic pulmonary tuberculosis. Two of the 51 were male nurses employed in the psychiatric division of the hospital and their disease was discovered during the 1932–33 survey. Since 1933 the male nurses have had health supervision independently of the Nurses' Health Service of the hospital. We will therefore omit the two male nurses from further discussion since we do not have records available of later cases in this group. The other 49 nurses were women whose ages ranged from twenty-one to fifty years. The average age was twenty-six years at the time of discovery of their disease. The total number of women nurses employed at some time and for varying lengths of service on the regular staff of the hospital during the period of the study was 2,149. In addition, there were 803 graduate nurses who worked in the hospital for short periods as graduate students. Thus, there were 49 cases of pulmonary tuberculosis found in a population of 2,952, an incidence of 1.7 per cent over a seven-year period. The discrepancy between this figure and the number found, namely, 8.3 per cent, during the one year when the entire nursing staff received routine roentgenographic examinations, is striking and indicates a relative ineffectiveness of the voluntary case-finding routine of the later period. The greater frequency of tuberculosis found in the survey of 1932–1933 may be explained in part, however, by the inclusion of older and more permanent members of the staff, some of whom had been associated with the hospital for some years before their lesions were discovered. The subsequent history of most of these has shown that their lesions were already well stabilized at the time of their discovery.

An analysis of the cases shows that 37, or 75.5 per cent, of the 49 cases were minimal; 11, or 22.5 per cent, were moderately advanced and only 1, or 2.0 per cent, was far advanced when the diagnosis was established. This is a moderately favorable distribution with preponderance of minimal stage cases. With a completely efficient case-finding program, it is

possible to find as high as 90 per cent or more of cases before they have progressed beyond the minimal stage. In an effort to attain such results the routine has now been established on a semi-obligatory basis with prompt examination of all new appointees and with provision for regular yearly reëxaminations.

Since we have been unable to assemble data showing what part of the staff had roentgenographic examinations during the period covered by the present study, no conclusions concerning the existence of an occupational hazard are possible. The records indicate, however, that most of the nurses in whom pulmonary tuberculosis was found had their lesion at the time of their employment. Among the nurses who developed the disease during their term of service in the hospital, there was no evident preponderance of those who have served on the tuberculosis ward. This ward, as has been stated, is small and a strict isolation technique is employed.

We have, in this report, regarded all definite and persistent pulmonary infiltrations as significant. There were, of course, especially among the older nurses, a number with arrested lesions and in the majority the disease was latent, in the sense that the only evidence of its presence was the roentgenographic shadow. During the greater portion of the period covered, there was no fixed policy regarding the clinical management of the nurses in whose films signs of pulmonary tuberculosis had been found, and selection of cases for treatment was in most instances not made by the authors. In general, as soon as a lesion had been discovered, the patient was examined by some member of the hospital staff and his recommendations were followed.

Four of the 49 cases had been diagnosed and treated previously, leaving 45 who had not known of their disease prior to their association with the hospital. Of these, 5 left the hospital after discovery of their lesion and no further record was obtained. Nineteen stopped work and were placed under treatment either in the hospital, in a sanatorium or at home, within a few days to a month after the diagnosis was made; 10 of these had symptoms while the other 9 were minimal, asymptomatic cases. Twenty-one were allowed to continue at work under observation. They all had minimal lesions and symptoms were either totally absent or so slight as to have been regarded as insignificant by the physicians who examined them. Sputum was either absent or negative for tubercle bacilli. Examination of the gastric contents for tubercle bacilli was made only in a minority of this group; it was positive on guinea pig inocula-

tion in one. Erythrocyte sedimentation rates and differential white blood cell counts were normal in most instances in which they were recorded. In 8, or about a third of the 21 cases, the disease progressed. In the remaining 13, there was no evidence of progression in an average follow-up period of twenty-four months. It is of interest to note that the average age of those whose lesions progressed was twenty-five years, while the average of those whose lesions remained stationary was twenty-nine and one-half years. In most of the former the spread of disease was relatively slight before it was discovered, but there were several who reached a moderately advanced stage before the progression was recognized and treatment instituted. Although progression occurred in only a little over a third of untreated, minimal, asymptomatic cases, it is to be emphasized that this was in a selected group which included older persons whose disease had been arrested for some years. Another selective factor was the exclusion of a number of younger nurses with asymptomatic, minimal lesions who received treatment without waiting for conclusive evidence that the lesions were progressive. Had all of the younger nurses with asymptomatic, minimal disease been allowed to continue at work under observation the proportion of progressions would probably have been considerably higher, even in the relatively short follow-up period of two years.

It is our impression that, as claimed by Amberson (5), asymptomatic tuberculosis in young adults eventually progresses in the majority of instances and should always be treated early. A definite policy has, therefore, recently been followed of recommending prompt treatment for all patients under thirty years of age in whom an infiltrative lesion has been discovered, regardless of the presence or absence of symptoms, the extent of the lesion or the results of sputum examinations and other laboratory procedures. We regard lesions presumed to be primary or first-infection type as of equally serious significance as those which appear to be the result of endogenous or exogenous reinfections.

SUMMARY

1. The results of routine tuberculin tests and roentgenographic chest examinations of a group of medical students, nursing students and graduate nurses are reported.

2. The incidence of pulmonary tuberculosis, inclusive of cases with arrested disease, was found to be 2.0 per cent for the medical students and 1.1 per cent for the nursing students. The incidence of new lesions,

developing after the initial roentgenographic examinations of entering students, was 0.35 per hundred per year among medical students and 0.18 per hundred per year among nursing students.

3. The incidence of pulmonary tuberculosis among graduate nurses was found to be 8.3 per cent, inclusive of cases of arrested disease, in a survey conducted during one year of all nurses employed on the hospital staff. This high incidence is attributable partly to the age composition of the group.

4. The cumulative incidence of cases of pulmonary tuberculosis diagnosed among graduate staff nurses over a period of six and three-fourths years was 1.7 per cent. The majority of the cases were found by means of routine roentgenographic examinations and 75 per cent were of minimal extent. Periodic routine roentgenographic examinations were, however, not obligatory during most of this period.

5. Of 21 cases of minimal, asymptomatic pulmonary tuberculosis in graduate nurses who were allowed to continue at work under observation, there were 8 in whom progression of the disease occurred during an average observation period of two years. Such progressions occurred most frequently in nurses who were under thirty years of age.

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LYMPHO-HAEMATOGENOUS TUBERCULOSIS[1, 2]

SAMUEL COHEN

In our contacts with tuberculous patients, we frequently consider tuberculosis simply as a localized disease process affecting chiefly the lungs and tend to lose sight of the broader ramifications of the ailment. However, the concept of tuberculosis as a systemic infection is fundamental for a dynamic interpretation of many of its aspects. In this paper, the clinical and roentgenological approach to the diagnosis of some of the salient features of lympho-haematogenous tuberculosis is stressed. I realize that this is a hazardous undertaking for there are many controversial problems with regard to this subject for which even the pathologist and bacteriologist have no answers as yet. Limited space will permit only a kaleidoscopic view, but this may be adequate to visualize the significance and potentialities of lymphatic and haematogenous disseminations.

SUMMARY OF STUDY

This study is based on a review of 246 cases that died of tuberculosis on the Tuberculosis Service of the Jersey City Medical Center during a period of four and one-half years (June, 1934 to December, 1938 inclusive); 78 per cent were white patients and 22 per cent were colored; 55.6 per cent were males and 44.4 per cent were females. Of the entire group, 45, or 18.3 per cent, showed during life gross clinical or roentgenological evidence of lympho-haematogenous spread of their disease. These were noted during routine but careful observation. I have been very cautious in the selection of cases belonging to this category and I believe 18.3 per cent represents a conservative estimate. There were a number of patients, for example, with pulmonary tuberculosis and cervical or axillary adenitis in whom there was more than reasonable assurance that the latter had a tuberculous aetiology also, but they were

[1] From the Hudson County Tuberculosis Hospital, Dr. B. S. Pollak, Medical Director, and from the Tuberculosis Service at the Jersey City Hospital, Jersey City, New Jersey.

[2] Read in part at the Metropolitan Sanatorium Conference, Cornell University Medical College, New York City, October 9, 1940.

excluded because of lack of biopsy proof. Several other cases gave a strong impression of haematogenous tuberculosis from the roentgenogram of the thorax but, due to inadequate serial films for comparison, were omitted. It is also likely that some of the far advanced pulmonary cases on admission may have arisen from the progression of originally haematogenous parenchymal foci.

The total number of autopsies for the entire 246 cases was 84; of the 45 diagnosed clinically as belonging to the lympho-haematogenous group, autopsies were obtained in 20, or 44 per cent, and confirmed the impression of such spread; of the remaining 201 cases, there were 13 in whom an antemortem diagnosis of haematogenous dissemination was not made but necropsy revealed such evidence. In other words, the autopsy incidence for haematogenous spread was 33 out of 84, or 39 per cent; the incidence based on conservative clinical and roentgenological studies was 18.3 per cent. However, this discrepancy is not so disconcerting when it is realized that many of the lesions were found at autopsy in deep seated organs which are beyond clinical examination and also that a number of haematogenous foci were noted on histological study only.

The distribution of the 246 patients according to age at death and duration of illness is shown in the accompanying graphs (figures 1 and 2). It is, of course, well known that the exact onset of tuberculosis is difficult to determine. Symptoms appear after the disease has become well established and, for this reason, in accepting the patient's history errors were inevitable. Wherever available, abnormal, antecedent roentgenograms always took preference over the patient's story in compiling the data for the onset of the disease. In 11 cases, no estimate of length of illness could be obtained. It is interesting to record concerning the haematogenous group of the clinically diagnosed 45 cases:

1: That 26 were white patients, or 13.6 per cent of the total white cases, and 19, or 35 per cent, (or about two and one-half times as many proportionately) belonged to the Negro race.

2: That the ratio between males and females was about 2 to 1; 29 males and 16 females.

3: That the greatest mortality for the entire 246 cases was in the ages between twenty and thirty-nine years; 61.3 per cent of the haematogenous cases (average age, twenty-seven years) and 53.2 per cent of the nonhaematogenous were in this age group.

4: That in 52.2 per cent of the haematogenous cases the duration of illness

was one year or less and in 34.8 per cent of the nonhaematogenous cases it was the same period. A disparity is to be expected, of course, for the intervention of serious extrapulmonary haematogenous lesions (particularly menin-

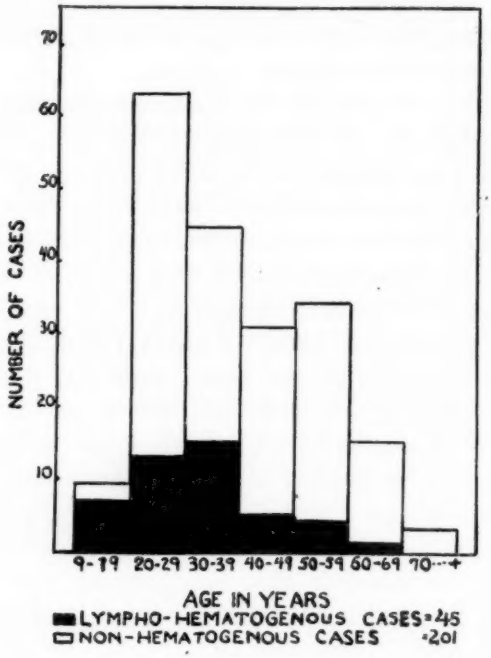


FIG. 1

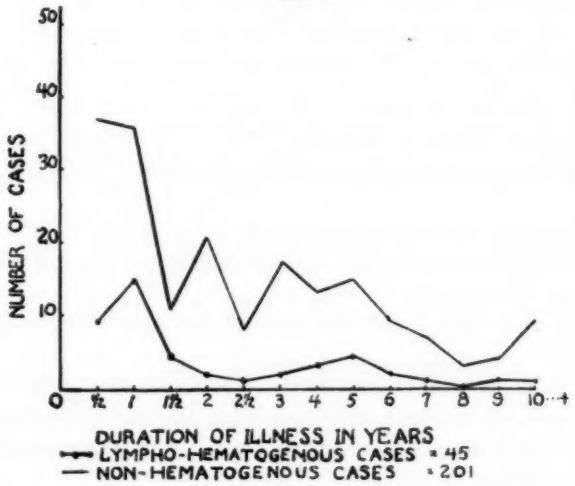


FIG. 2

gitis which occurred in 14, or 31 per cent, of the cases) may reduce the span of the tuberculous disease process considerably.

5: A diagnosis of haematogenous pulmonary tuberculosis based on clinical and available roentgenological observations was made in 29 (64.4 per cent) of the group, or in 11.8 per cent of the entire 246 cases. The criteria used for the diagnosis of haematogenous pulmonary foci were:

(a) The roentgen appearance of more or less discrete and evenly distributed lesions, particularly in the upper parts of both lungs; in a generalized involvement, the lungs, of course, are seeded rather uniformly from apex to base. The lesions may be of miliary size or larger and of varied specific reaction—exudative, fibrotic, calcific.

(b) The frequent absence of older lesions from which a bronchogenic spread could have originated.

(c) The frequent occurrence of pleurisy with effusion or evidence of old pleuritis and bronchopulmonary or mediastinal adenopathy detected on the X-ray film.

(d) Abdominal films for possible visualization of calcified nodes or calcified tubercles in the spleen may yield confirmatory information for haematogenous spread.

(e) The frequent presence of extrapulmonary haematogenous lesions, particularly in the meninges, spleen, bones and joints and genitourinary tract. A study of frequent serial roentgenograms of the chest with particular attention to the aspects outlined above, together with the indirect evidence obtained by a thorough search for parapulmonary foci constitute the best clinical approach for the diagnosis of haematogenous pulmonary tuberculosis, especially in the chronic cases. Bronchogenic miliary or larger nodules, resulting particularly after haemoptysis, are most often confused on the X-ray film with haematogenous pulmonary involvement.

An attempt has been made to group the 45 cases mainly according to the following forms and phases of haematogenous tuberculosis some of which have been particularly emphasized by Grethmann (1).

(*1*) *Miliary Tuberculosis:* The distribution is focal or generalized; focal miliary pulmonary tuberculosis is usually confined to the upper segments of the lungs and is bilateral and symmetrical; it is acute, subacute or chronic. The term miliary connotes the size of the lesion (millet-seed). The terms acute, subacute and chronic refer to the time period of dissemination and not to the time period of the growth of a tubercle.

(*2*) *Medium-sized Nodular Tubercles:* The distribution and duration are as above.

(*3*) *Protracted Multiform Tuberculosis*

(*4*) *Transitional Form of Haematogenous Pulmonary Tuberculosis*

(*5*) *Phthisis with Extrapulmonary Haematogenous Lesions:* In other cases the clinically predominant lesion or lesions may be outside of the lungs which may reveal no foci or apparently inactive foci.

While clinical manifestations may be varied and atypical and cases cannot always be pigeon-holed, these forms represent certain dominant biological features and thus serve a useful function. It is not to be assumed that a rigid classification of different types of haematogenous tuberculosis is being proposed. Tuberculosis being evolutionary and not static, some degree of overlapping into one or more of the groups is almost inevitable. The purpose is to utilize certain reflections and observations as helpful tools to increase the acuity of the clinician for a better appreciation of the dynamic systemic phases of tuberculosis.

CASE REPORTS

Illustrative cases are appended, except in the first group which is the most familiar type of haematogenous tuberculosis and needs no exemplifying presentation here.

Acute or Subacute Generalized Haematogenous Tuberculosis: There were 7 patients in this group; 6 white and one colored; 4 females and 3 males; all had generalized miliary tuberculosis of the lungs and 5 developed meningitis. The average duration of the illness was five months. Three had associated pleural effusions and the spleen was palpable in 2.

All had negative sputa examinations for tubercle bacilli. These cases are comparable to an acute or subacute bacteraemia. Apparently a large shower of organisms and toxins enter the vascular system in a rather fine suspension and produce the characteristic findings. Autopsies were obtained in 2 cases.

Chronic Miliary Tuberculosis: Four patients, all white males, belonged to this group. The duration of illness ranged from two to twelve years. All had roentgenographic evidence of haematogenous, pulmonary, miliary tuberculosis; 3 showed focal, bilateral, symmetrical seeding at first, with subsequent increase on serial films. Three patients had superficial adenopathy, 2, pleural effusions, 2, enlarged spleen; other extrapulmonary haematogenous lesions noted among the group were meningitis, Pott's disease, tuberculosis of knee, epididymis and prostate and calcified abdominal lymph nodes. Autopsies were obtained in 3 instances.

Case 1: W. B., age fifty-three, an emaciated white male, was admitted to the Tuberculosis Service March 22, 1935. In 1910, he developed anorexia and gaseous eructations which persisted for many years. A diagnosis of gastric ulcer was made in 1926 and dietary treatment was instituted. He was hospitalized on the Medical Service in April, 1933 with the symptoms of abdominal pain, diarrhoea and tarry stools. A chronic cough had been present for eight years. The roentgenogram of the chest (April 28, 1933) (figure 3) revealed rather symmetrical fine nodular and linear infiltrations particularly in the upper two-thirds of the pulmonary fields with pleuritis on the left. Five weeks before his last admission, the patient developed marked anorexia with loss of 30 pounds. The right lung showed dulness at apex anteriorly and posteriorly with an occasional râle and diminished breath sounds throughout. The left lung revealed dulness over the upper lobe with few râles below the clavicle and dulness with decreased breath sounds at the base posteriorly. The heart sounds were of poor quality; the spleen was felt below the costal margin. Firm enlarged nodes were felt in the neck, left axilla and both inguinal regions. The gastrointestinal work-up showed a markedly dilated stomach with a barium residue at six and twenty-four hours. The pylorus was rounded and obstructed, apparently due to an old scarred ulcer.

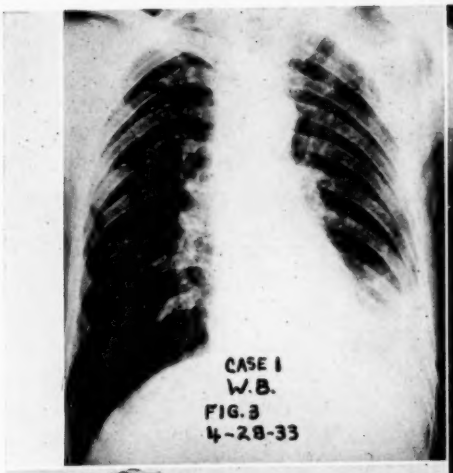
On the chest film (April 3, 1935) (figure 4) was noted an increased, disseminated, symmetrical fine mottling, right thickened interlobar fissure and left flattened diaphragm with obliterated sulcus. The sputum was negative for tubercle bacilli. The patient's course was unfavorable and he died April 5, 1935. An autopsy was done.

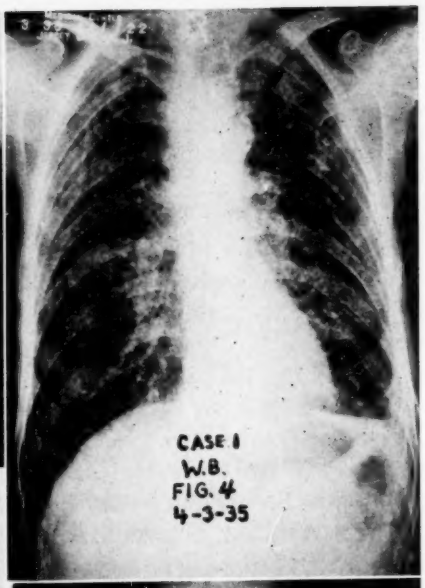
Final Anatomical Diagnosis: Lungs: haematogenous miliary tuberculosis, also confluence of foci in some areas, emphysema, bronchiectasis, anthracosis, bilateral adhesive pleuritis (figure 5); miliary tuberculosis of spleen, kidneys, liver; tuberculosis of axillary, inguinal, mesenteric nodes; right subdiaphragmatic tuberculous abscess; tuberculous osteomyelitis of the eleventh right rib; prepyloric nontuberculous ulcer and duodenitis.

Comment: Available roentgen evidence two years before death was characteristic of haematogenous miliary tuberculosis. This was a rather incidental and unexpected finding, for the gastrointestinal symptoms were paramount. In 1935, the involvement was much more extensive. The feeding focus is a matter of conjecture, but the tuberculous abdominal adenopathy may have been the source.

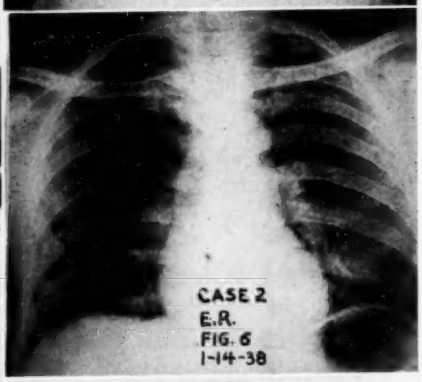
Subacute or Chronic Medium-sized Nodular Haematogenous Tubercles: There was only one case in this group.

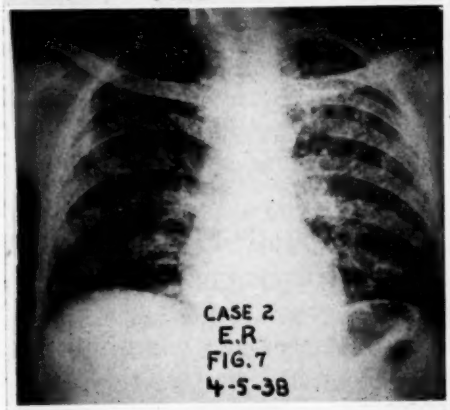
Case 2: E. R., a colored male, age forty-three, entered the Medical Service January 3, 1938, and was transferred to the Tuberculosis Service February 9,

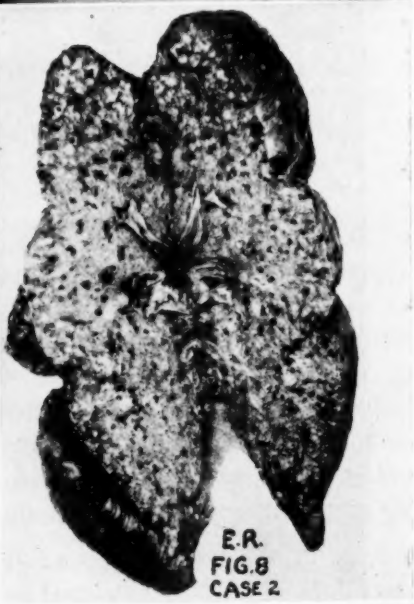

CASE 1
W.B.
FIG. 3
4-28-33

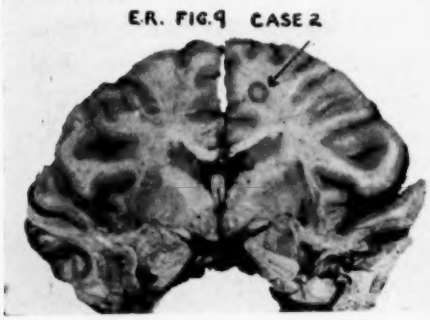

CASE 1
W.B.
FIG. 4
4-3-35

W.B.
FIG. 5 CASE 1


CASE 2
E.R.
FIG. 6
1-14-38


CASE 2
E.R
FIG. 7
4-5-38


E.R.
FIG. 8
CASE 2


E.R. FIG. 9 CASE 2

FIGS. 3-9

1938. He had been a foundry worker for the past twelve years. Six months before admission the patient developed epigastric pain, nausea and loss of weight. He visited the Medical Clinic in the latter part of September; a chest roentgenogram taken October 1, 1937 showed some increase in linear markings with fine nodular foci in the third to fifth interspaces on the left. There was no definite evidence of silicosis despite a positive occupational history. He returned to the clinic in January and hospitalization was advised on the Medical Service, the tentative diagnosis being gastric crisis or peptic ulcer. The gastrointestinal roentgenological study was negative. However, the chest film of January 4, 1938 (figure 6) revealed a densely packed bilateral miliary seeding extending from the apices to bases. Cough was slight with scanty sputum which was negative for tubercle bacilli on several occasions. A high irregular fever, at times to 104°F., persisted throughout and was associated with a leucopenia. The lungs were essentially negative on physical examination. There were palpable cervical and inguinal nodes. The spleen was not felt. Another roentgenogram of April 5, 1938 (figure 7) showed a definite increase and confluence in many areas of the nodular foci. During the second week of May, 1938, he developed meningitis and died May 26, 1938. An autopsy was performed.

Final Anatomical Diagnosis: Haematogenous miliary and medium-sized nodular tubercles; lungs: miliary and predominantly conglomerate lesions, up to 4 mm. in diameter, extending from apices to bases (figure 8); similar lesions on pleural surfaces; anthracosis and emphysema; enlarged, partly caseous infratracheal and paratracheal lymph nodes; brain (figure 9): basilar meningitis and tuberculoma, 4 mm. in diameter, in left frontal lobe; liver and spleen: numerous nodular lesions from 1 to 3 mm. in diameter; enlarged paraportal and parapancreatic nodes; kidneys: miliary tuberculosis; right adrenal gland: caseous lesions from 2 to 10 mm. in size.

Comment: The clinical and pathological findings may be interpreted as wide-spread, repeated haematogenous implantations in the lungs, among other organs, with confluence in many areas and formation of medium-sized nodular foci. Had this patient lived several months longer, it is very probable that further progression of the pulmonary lesions would have led to cavitation and bronchogenic dissemination. This case appears as an intermediate step in the transition from haematogenous into bronchogenic pulmonary tuberculosis. The development of a fatal meningitis apparently interrupted the completion of this transition.

Protracted Haematogenous Multiform Tuberculosis: This comprised the largest group, 17 cases (10 females and 7 males) including one case

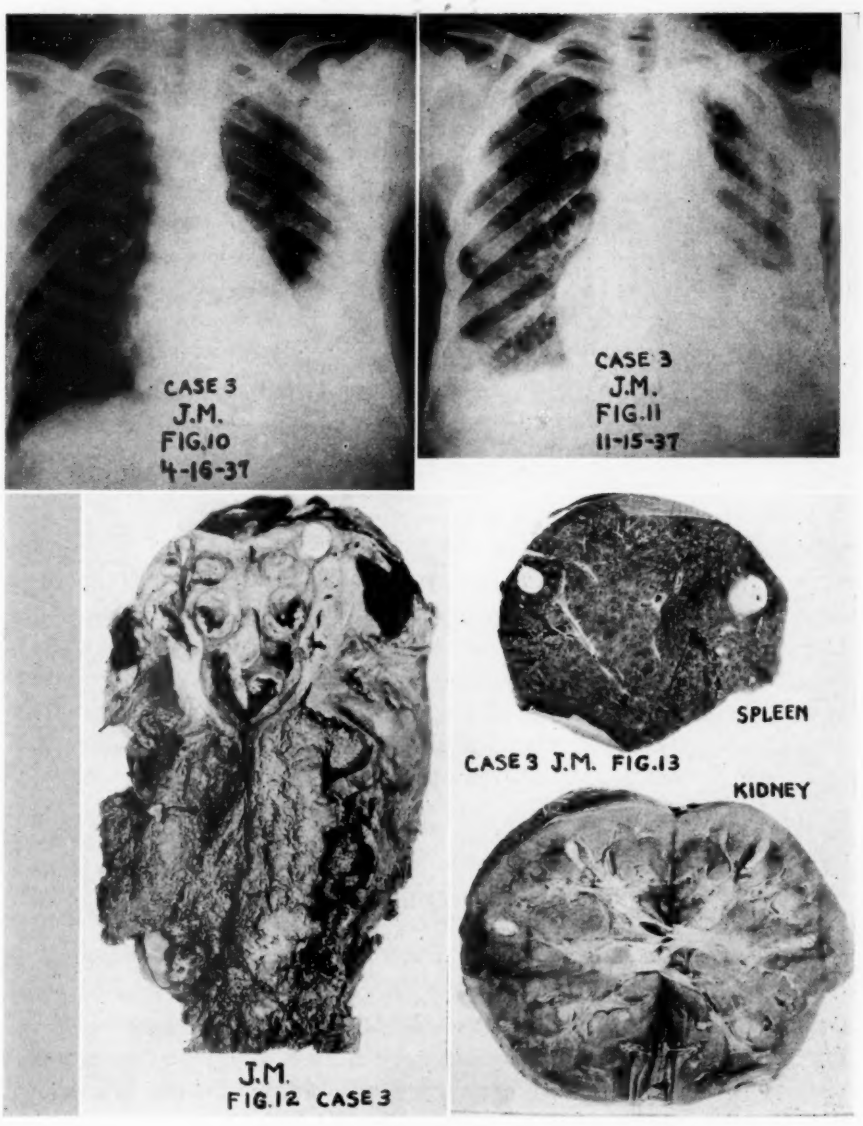
which belonged to the sarcoid class. The essential features of this type of haematogenous dissemination have been mentioned in an earlier report (2). Fifteen patients were colored and 2 were white. The youngest individual was eleven years and the oldest thirty-six; the average age was 25.5 years. In 10 cases, the duration of illness was six months to one year; in 3 patients, it was between fifteen months and two years and in 4 instances it ranged from six to nine years.

This form of haematogenous tuberculosis, which has been elaborated by Grethmann (3) as a clinical and morphological entity, is of much interest and is seen most often in the colored races. The bacillary and toxic implantations into various structures occur in successive crops, usually over a period of many months, producing lesions of varying size and age, ranging from miliary to large conglomerate nodules—hence the term multiform. The various doses may come from the same or different foci which are usually caseous lymph nodes. The notable findings in these cases are wide-spread adenitis and multiple serositis. The involvement of the spleen is almost pathognomonic as an indicator at necropsy of such a protracted dissemination with its lesions of varying forms and dimensions.

Case 3: J. M., age twenty-eight, a colored male was admitted to the Medical Service April 14, 1937 and transferred to the Tuberculosis Service June 15. Two weeks before admission, cough and pleuritic pain in left axilla developed. The roentgenogram (April 16, 1937) (figure 10) showed a density at the left hilum probably due to bronchopulmonary nodes, and also a left-sided pleural effusion. Three thoracocenteses (between May 10, 1937 and June 1, 1937) yielded yellow to greenish fluid, sterile on culture; small amounts of air were given. The sputum, scanty at first and negative for tubercle bacilli, later increased to one ounce and became positive. Physical signs indicated a parenchymal lesion in the left lower lobe which could not be dissociated from the roentgen shadow produced by the fluid. Artificial pneumothorax was continued until October, 1937 and then stopped because it was pocketed and a tuberculous empyema formed. However, haemoptyses occurred in December and refills were resumed and carried out when indicated until the patient's death.

In August, 1937, the patient developed pain and a persistent swelling over the left wrist which was immobilized. X-ray studies were negative until January, 1938 when some destruction of the styloid process of the ulna was noted together with soft tissue swelling. This was considered tuberculous. In October, 1937 a cold abscess appeared over the upper end of the sternum. X-ray films showed no bony lesion of the sternum, dorsal vertebrae or ribs.

A persistent sinus followed its incision. The autopsy subsequently revealed that this tract communicated with the left empyematous pleural cavity



FIGS. 10-13

through openings in the mediastinal pleura and intercostal fascia. The spleen was palpable. Bilateral axillary nodes were also felt. The chest

film (November 15, 1937) (figure 11) showed scattered mottling on the right with flattened diaphragm and an obliterated costophrenic angle indicative of pleuritis; a hydropneumothorax, collapsed portion of the left lung and a few honeycombed areas were seen in the first interspace. The mediastinal shadow was wider than normal due to adenopathy. The patient became progressively weaker, remained febrile throughout and died February 5, 1938.

Final Anatomical Diagnosis: Protracted multiform lympho-haematogenous tuberculosis; lungs: haematogenous miliary and small nodular tuberculosis; cavitation with bronchogenic spread; anthracosis and emphysema; bilateral adhesive pleuritis with marked caseation of left pleura and extension to diaphragm; tuberculous fistulous sinus between left pleura and chest wall (figure 12); miliary and medium-sized nodules of pericardium and peritoneum; caseous lesions varying from 2.0 mm. to 1.5 cm. in spleen, liver, kidneys (figure 13); caseous bronchopulmonary mediastinal, mesenteric adenopathy; chronic ulcerative tuberculosis of ileum.

Comment: The clinical impression conveyed by the case is one of a chronic or recurrent tuberculous bacillaemia. Consequently the age and size of the lesions were variable as noted at necropsy. The true extent of serous membrane involvement and the degree of adenopathy were revealed by the postmortem examination. The caseous pleuritis most likely resulted by direct extension from the matted caseous mediastinal and bronchopulmonary nodes. Primary lymphatic spread with secondary invasion of the blood-stream probably represented the route of metastatic dissemination.

Transitional Form of Haematogenous Pulmonary Tuberculosis: There were 9 cases of haematogenous pulmonary tuberculosis which showed progression with ultimate cavity formation, bronchogenic spread and positive sputum. The clinical, roentgenological and pathological features of such cases have been reported in a previous publication (4). Haematogenous (interstitial) lesions may increase in size, become caseous, excavate and discharge tubercle bacilli into the bronchi; thus, there can be produced a mixture of haematogenous and bronchogenic lesions in the lungs and, at death, the latter may predominate. Absolute histological proof of this evolution from haematogenous into bronchogenic tuberculosis may be very difficult to obtain in the late stages. The correct sequence of events may frequently be reconstructed by study of the serial roentgen films and the conversion of the sputum from negative to positive.

The cases assigned to this category, with one exception, belonged to

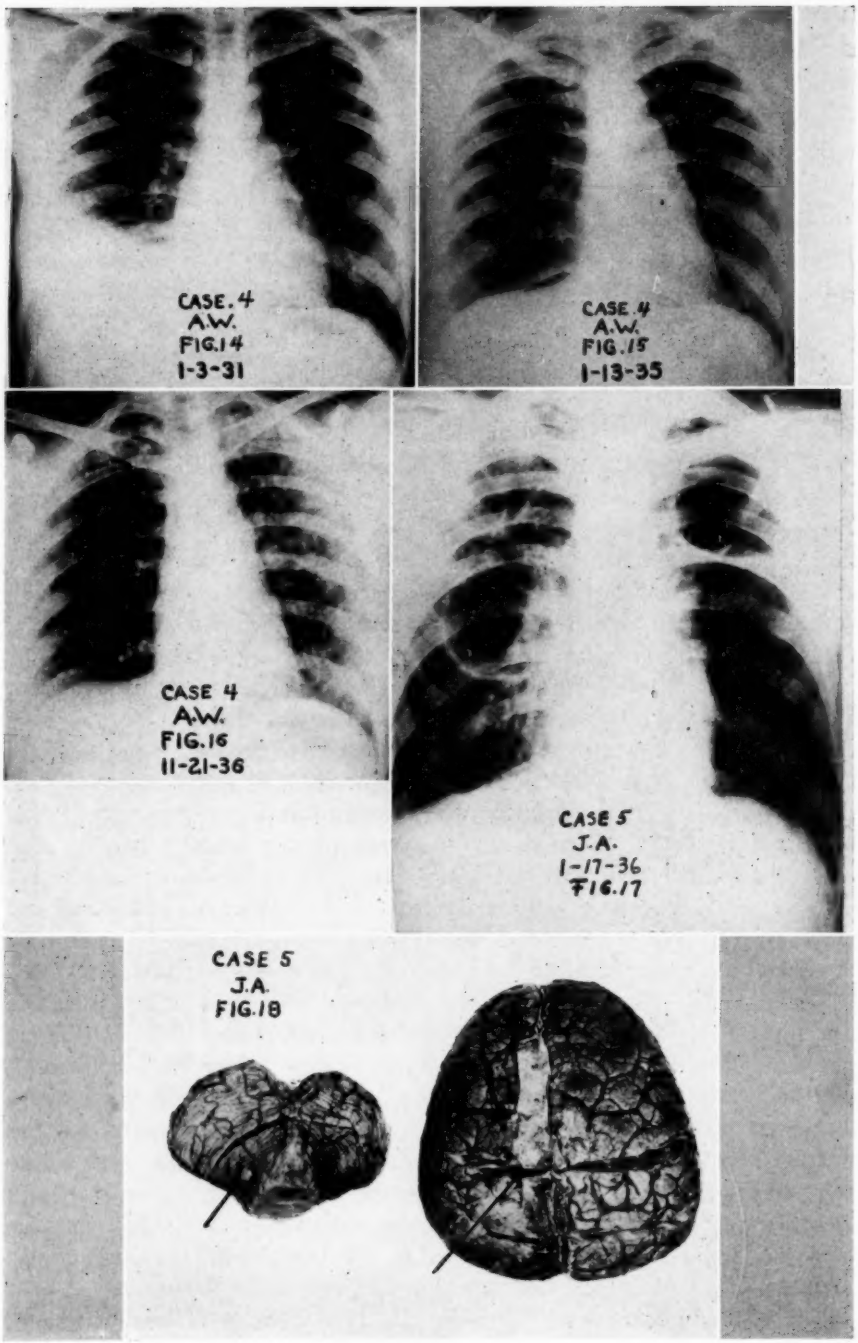
the protracted multiform group. The pulmonary findings were sufficiently striking to segregate them into this additional interesting and evolutionary phase of the disease process, although, strictly speaking, I admit that they do not constitute another "form" of haematogenous tuberculosis. Seven were colored and 2 were white patients. Their ages ranged from eleven to fifty-seven years, and the duration of illness from eleven months to twelve years. Autopsies were performed on 4 patients.

Case 4: A. W., a white female nurse was twenty years of age at the time of her first admission to the Tuberculosis Service on June 29, 1932. She had a total of six admissions to the hospital. The significant features of her illness were as follows: The first roentgenogram of the chest taken in September, 1930 was negative. In December, 1930 she developed right pleuritic pain and the film of January 3, 1931 (figure 14) showed a pleural effusion. She "took things easy" for several months but because of weakness, dry cough and some loss of weight entered the hospital. The film of June 30, 1932 revealed infiltration of the predominantly productive linear type on both sides from the apices to the second anterior ribs. She returned home May, 1933, continued with bed-rest until September, 1933 and resumed her nursing duties in July, 1934.

In the latter part of September, 1934 she noted frequency of urination, dysuria, haematuria and pain over the left lumbar region. No cough or expectoration were present. Physical examination of the lungs revealed slight dulness in both upper lobes posteriorly. The chest film of October 6, 1934 showed productive, symmetrically distributed infiltrations in the upper thirds of both lung fields. The sputum was negative for tubercle bacilli. The urine showed albumin and red blood cells. On cystoscopic examination October, 1934, congestion and oedema around the trigone of the bladder and in the ureteral orifices were found; on the posterior bladder wall were a number of tubercles. Urine obtained by catheterization of the left ureter revealed tubercle bacilli. The pyelogram showed furred edges and filling defects in the upper two calyces. The function of the right kidney and its roentgen visualization were normal. The left kidney, removed in December, 1934, was enlarged and almost completely replaced by tuberculous excavations. The chest plate of January 13, 1935 (figure 15) presented a mixture of fine nodular and linear productive foci on the right side from the apex to the third anterior rib and on the left side down to the fourth anterior rib.

In February, 1935 the patient noted she was limping on her left leg. By May, pain appeared in the coccygeal region. Tuberculosis of the left sacroiliac joint was diagnosed which was immobilized in a hip spica plaster cast.

The last admission was November 21, 1936 because of loss of weight,


CASE. 4
A.W.
FIG.14
1-3-31
CASE. 4
A.W.
FIG. 15
1-13-35
CASE 4
A.W.
FIG. 16
11-21-36
CASE 5
J.A.
1-17-36
FIG. 17
CASE 5
J.A.
FIG. 18

FIGS. 14-18

pleuritic pain in left chest and increased cough with scanty expectoration. The right lung showed coarse râles over the upper lobe; on the left side were noted bronchial breathing in the supraclavicular fossa, diminished breath sounds posteriorly and coarse râles in the upper lobe. The chest film (November 21, 1936) (figure 16) showed infiltrations throughout the left lung; the infiltrations were confluent in many areas and intervening small areas of highlight were present, particularly in the first interspace. The right lung presented a slight increase in the lesion as compared to the 1935 film. The first positive sputum was reported in February, 1937. The last film, taken June 21, 1937, showed an increase in the infiltrations in both lungs with larger annular shadows in the upper third of the left lung. The spleen was not palpable. Frequent recurrence of urinary symptoms developed and albuminuria persisted. The patient became progressively weaker and died July 10, 1937 at the age of twenty-five years. A postmortem was not obtained.

Comment: A pleural effusion marked the clinical onset of the patient's illness. This is a frequent event in haematogenous tuberculosis. The parenchymal involvement was at first bilateral, more or less symmetrically distributed and in the upper portions of the lungs which is typical for haematogenous tuberculosis. Gradual progression occurred with cavitation, finally, and a superimposed bronchogenic extension as noted on the last films. The sputum which had been negative for several years ultimately became positive for tubercle bacilli. The extrapulmonary lesions in the kidney and hip rounded out the general picture of haematogenous seeding and gave added weight to the endogenous origin of the pulmonary foci.

Phthisis with Extrapulmonary Haematogenous Lesions: Sixteen cases, at the time of admission, had roentgen evidence of phthisis and, in all but one, the sputum was positive for tubercle bacilli. Five of these patients also showed on the chest film or developed a superimposed, terminal, acute, haematogenous, miliary tuberculosis of the lungs; 7 died with tuberculous meningitis. Other extrapulmonary haematogenous lesions noted in this group involved the epididymis, prostate, female adnexa, knee, spine, humerus and clavicle. The spleen was palpable in 2 cases. The average duration of illness for the entire group was approximately two and one-half years. How many of these cases may have started with haematogenous pulmonary foci, which by the time of admission had progressed to phthisis, cannot be stated.

While most of the patients presented a chronic course, they could not

be properly classified with the protracted multiform group because they lacked the typical clinical characteristics. It is interesting to note also that of the 16 patients (14 males and 2 females) 15 were white and one colored; the ratio between the two races being the reverse of that in the protracted multiform group. Autopsies were obtained in 5 cases.

Case 5: J. A., white male, age thirty-two, had two admissions to the Tuberculosis Service. The onset was in 1932 with a haemoptysis. On his first admission in July, 1935 the X-ray film showed bilateral cavernous and infiltrative lesions. The sputum was positive and he was transferred to another institution in October, 1935 but was readmitted to the Medical Center on May 16, 1936 in a delirious state. The story obtained later was that loss of weight had been marked during the past two months with frequent headache since May 9. Symptoms and signs, confirmed by study of the spinal fluid, indicated tuberculous meningitis. The patient died May 18, 1936. The roentgenogram of January 17, 1936 (figure 17) obtained from the other hospital showed giant cavities in both lungs, with scattered small nodular foci.

Final Anatomical Diagnosis: Lungs: chronic bilateral ulcerative tuberculous and bronchogenic spread; some discrete miliary haematogenous lesions; anthracosis and emphysema; bilateral adhesive pleurisy; several anthracotic and partly caseous infra- and paratracheal lymph nodes; brain: basilar meningitis and tuberculoma (9 mm. in diameter) in right cerebellum and a slightly smaller one in the right parietal lobe (figure 18); focal miliary tuberculosis of spleen and kidneys; amyloidosis of spleen and liver.

Comment: Next to acute generalized miliary tuberculosis, this type of case is probably most commonly appreciated as signifying haematogenous dissemination. The patient presented evidence of bilateral cavitary tuberculosis. A chest plate was not obtained on his last admission which extended only two days. It is interesting to note that postmortem examination disclosed a terminal haematogenous miliary tuberculosis, although the intracranial lesions were of large size and therefore most likely antedated the final spread.

I hope I have not conveyed the impression that haematogenous dissemination necessarily ends fatally. Postmortem records in the Medical Examiner's Office of any large city will reveal a considerable incidence of recent and old haematogenous lesions in persons who have died from other causes. An interesting publication, from another source, namely a large general hospital, is that by Reichle and Work (5) who reviewed the autopsy findings of 452 consecutive cases at the

City Hospital, Cleveland. In this group of patients who died from a variety of causes 91, or 20.1 per cent, were found to show evidence of healed miliary tubercles in spleen, liver or kidney which became involved through the haematogenous route.

SUMMARY

1. In a series of 246 consecutive patients who died of tuberculosis, 45, or 18.3 per cent, showed during life clinical or radiological evidence of lymphatic or blood-stream dissemination of the disease. This is believed to represent a conservative estimate. Negroes showed this spread about two to one-half times more frequently than white patients. The ratio of males to females was almost two to one. The age of the patients and duration of illness are recorded.

2. A diagnosis of haematogenous pulmonary tuberculosis, based on clinical observation and X-ray films, was made in 29, or 64.4 per cent, of the group or in 11.8 per cent of the entire 246 cases. The criteria used in making the diagnosis are mentioned. The chronic form of haematogenous pulmonary involvement was encountered more frequently than the acute generalized one.

3. The 45 cases have been arranged into several groups representing various forms and phases of haematogenous tuberculosis. Illustrative cases are reported.

4. The concept of tuberculosis as an evolutionary and systemic disease is stressed.

I am indebted to Dr. A. Gnassi, Pathologist of Jersey City Medical Center, for his advice and coöperation.

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GASTROINTESTINAL COMPLICATIONS IN PULMONARY TUBERCULOSIS[1]

LEO L. HARDT AND SEYMOUR J. COHEN

In this study, we wish to point to a few aspects that have been overlooked by most authors, and not sufficiently emphasized by others, in the literature reports on similar material. We refer particularly to the autopsy findings of gastric lesions in our series that tend to confirm the gastroscopic studies concurrently carried on in our institution.

About two-thirds of the patients entering the Municipal Tuberculosis Sanitarium are found to have far advanced pulmonary tuberculosis, and about 20 per cent of the entire group have gastrointestinal complaints. In such a group the gastrointestinal complications assume an important rôle in the successful treatment of the pulmonary lesions. It is of utmost importance to differentiate early between gastrointestinal organic lesions and functional disorders and, if organic, between tuberculous and nontuberculous lesions, so that we may treat them adequately and the pulmonary disease may be combated more successfully. With this in mind, an attempt has been made to study all patients complaining of gastrointestinal symptoms and to treat any specific lesions found, thus building up their general resistance.

This paper represents a study of the gastrointestinal findings in 1,000 autopsies covering the period from 1917 to 1937, and of 1,000 clinical cases referred to the gastrointestinal department during the past seven years, of which latter group 102 cases came to autopsy. In these 102 cases clinical-pathological correlations are made (see table 1). The clinical cases and the autopsy examinations are grouped into those suffering from tuberculous and nontuberculous lesions of the gastrointestinal tract.

Goldberg, Sweany and Brown (1) reviewed 230 autopsies done at the Municipal Tuberculosis Sanitarium in 1928; in our study we have included their series of cases. We wish to point out in connection with their report the frequent changes in the gastric mucosa, suggesting a

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high incidence of gastritis; they, however, did not allude to the clinical significance of their findings. Another significant observation was that 84.8 per cent of their cases had tuberculous lesions of the gastrointestinal tract. Crawford and Sawyer (2), in a study of 1,400 postmortem examinations made at Fitzsimons General Hospital in Denver, Colorado, report 66.8 per cent tuberculous lesions of the gastrointestinal tract; and Cullen (3), in a review of 1,443 cases, found that 77.4 per cent showed intestinal tuberculosis.

Rousseff (4), in a careful study of the stomach in 8 cases of pulmonary tuberculosis without intestinal involvement, found that 7 had normal

TABLE 1

Clinical and pathological correlation of 102 cases

89 cases, clinical diagnosis verified by autopsy examinations

83	Tuberculosis of bowel
3	No gastrointestinal complications
2	Carcinoma of caecum
1	Carcinoma of lung

13 cases in which the clinical diagnosis differed from the pathological findings

	CLINICAL FINDINGS	AUTOPSY FINDINGS
1	Pelvic tumor	Carcinoma of ovary
1	Carcinoma of stomach	Carcinoma of liver
1	Tuberculosis of bowel	Tuberculous peritonitis
5	Tuberculosis of bowel	Amyloidosis
3	Tuberculosis of bowel	1 duodenal ulcer 1 gastric ulcer 1 perihepatitis and perisplenitis
1	Allergic diarrhoea	Tuberculosis of bowel
1	Pellagra	Tuberculosis of bowel with amyloidosis

stomachs and one an unimportant change. On the other hand, in 26 cases of pulmonary tuberculosis and intestinal tuberculosis, he found that all had definite changes in the stomach (acute parenchymatous, chronic interstitial gastritis, atrophy of the glands or amyloid degeneration). Cohen (5), in his study of 1,000 gastric analyses, has shown that, as the tuberculous process develops, there is a corresponding diminution of the gastric acidity. Achlorhydria occurs in about 7 per cent of these cases. Portis and Jaffé (6), in a review of 9,171 autopsies from Cook County Hospital from 1929 to 1936, found 339 peptic ulcers, or 3.7 per cent. Of these, 185 were gastric ulcers and 154 were duodenal;

29.2 per cent of the gastric ulcers and 41 per cent of the duodenal ulcers were diagnosed before death. In a previous clinical study comprising 617 cases, Hardt, Weissman, Coulter and Henrichsen (7) found the incidence of tuberculous enteritis to be closely parallel to the findings of Goldberg, Sweany and Brown. So have many other authors, among them Brown and Sampson (8) and Rubin (9). Many other authors have pointed out the importance of the rôle played by digestive disorders in pulmonary tuberculosis and all emphasize the necessity of their proper treatment during treatment of pulmonary tuberculosis.

GASTROINTESTINAL FINDINGS IN 1,000 AUTOPSIES COMPARED WITH 1,000 PATIENTS SEEN CLINICALLY

Ages in the two groups: In the series of 1,000 autopsies, there were 596 males and 414 females, ranging in age from one year to seventy-seven. The average age of the males was thirty-one years, and of the females twenty-six years. In the clinical group of 1,000 patients, there were 465 males and 535 females, from fourteen to sixty-nine years of age. The average age of the males was thirty-three years and of the females twenty-eight years. One hundred and two of the patients of the latter group came to autopsy.

Tuberculous enteritis: In the 1,000 who came to autopsy, tuberculous lesions of the gastrointestinal tract were noted in 71 per cent, while in the clinical group 78.3 per cent were diagnosed as having intestinal tuberculosis. Summarizing the series of 102 cases, we find that 92.1 per cent were diagnosed clinically as having intestinal tuberculosis, while at autopsy only 81.3 per cent had intestinal tuberculosis. Five cases that had been diagnosed as tuberculous enteritis were found at autopsy to have amyloidosis of the liver. The clinical symptoms and physical findings in this group frequently made it impossible to differentiate between the two conditions. Of 3 others that had been diagnosed as tuberculous enteritis, one had a duodenal ulcer, one a gastric ulcer (in both of these cases none of the typical peptic ulcer symptoms was present), and the third had nausea, vomiting and frequent attacks of diarrhoea, yet only a perihepatitis and a perisplenitis were found at autopsy. One case, mistakenly diagnosed as allergic diarrhoea because the diarrhoea appeared only after eating certain types of foods, was found at autopsy to have intestinal tuberculosis. In still another case of marked intermittent diarrhoea with skin lesions typical of pellagra the diarrhoea was diagnosed to be a consequence of pellagra, but at

autopsy a tuberculosis of the bowel with amyloidosis of the liver was found.

Perforations: Gastrointestinal perforations as a result of tuberculosis occurred in 23 instances in the combined three groups. Of these, 2 were in the oesophagus, one was in the stomach as a result of a tuberculous lymph node that had perforated into the stomach, 15 were in the intestines, and 5 were in the appendix. Since 1933 there has been only one perforation, a tuberculosis of the ileum. It therefore follows that better dietary management has resulted in a marked decrease in the number of perforations during the past few years. Forced feeding of patients has been abandoned by us in favor of a smooth, high-vitamin and relatively high-caloric diet.

In the nontuberculous lesions, there was one case of erosion of the oesophagus with perforation; 2 cases of gastric ulcer and 2 of duodenal ulcer had perforations. One gastric and one duodenal ulcer perforation had been operated upon and recovered, but the other 2 were not recognized until autopsy.

Peptic ulcer: In the autopsy series, gastric ulcer was found in 23 cases, 2 of which had healed and 2 of which had perforated; in addition there were 21 duodenal ulcers, 2 of which had perforated, making a total of 44 ulcers. This total of 4.4 per cent of peptic ulcers is slightly higher than the 3.7 per cent reported by Portis and Jaffé (6) in 9,171 autopsies done at Cook County Hospital.

In the clinical series, peptic ulcer was diagnosed or suspected in 94 cases. Of this group, 51 were considered duodenal ulcers because of their clinical history, physical findings and X-ray evidence. Two were considered questionable both according to history and X-ray studies. In diagnosing peptic ulcer we were guided by a combination of physical findings, clinical history and X-ray evidence. If only X-ray evidence were available, it was considered inadequate. In view of this premise, we were obliged to reduce the number of our considered cases to 51 duodenal ulcers, 16 gastric ulcers and one gastrojejunal ulcer, or a total of 68 cases of peptic ulcer. Since the incidence of gastric ulcers in the autopsy series was slightly higher than that of duodenal ulcers, and since our diagnoses showed three times as many duodenal ulcers as gastric ulcers clinically, this would indicate either that many of the gastric ulcers are less likely to give a typical ulcer syndrome, or that many of the gastric ulcers are not recognizable roentgenologically.

The apparent increase of peptic ulcers in the 1,000 selected clinical

cases over the selected autopsy examinations is probably due to the fact that the selected 1,000 clinical patients represent the normal 20 per cent of patients suffering from gastrointestinal symptoms; therefore, it would seem logical to expect a higher number of peptic ulcers in this group. Of the 102 clinical cases which came to autopsy, 3 of the 5 patients with peptic ulcers showed very few symptoms that could be considered typical peptic ulcer symptoms, which would lead us to conclude that the symptoms of gastric ulcers in pulmonary tuberculosis are frequently masked by the tuberculous lesions.

Benign tumors: In the series of 1,000 autopsies, benign gastric tumors occurred in 4 cases, of which 2 were fibromata of the pylorus, one an aberrant pyloric pancreas with adenoma on the wall of the pylorus, and one a calcified lipoma on the lesser curvature of the stomach. There were 3 cases of adenoma of the liver, 2 of lipoma of the liver, and 7 of haemangioma. There was one case of adenoma of the gallbladder. In the caecum, lipoma was found once, and polyps 4 times. In the colon polyps were found in 8 cases. There was one polyp of the oesophagus and 4 of the sigmoid.

Malignancies: In the series of autopsies there were 4 carcinomata of the stomach, 3 of which were primary, the patients' ages ranging from forty-one to fifty-eight years. One of these was a metastatic nodule from a carcinoma of the lung in a patient of fifty-seven years. Carcinoma of the pancreas occurred in one case. There was one metastatic nodule on the duodenum from a carcinoma of the lung, and there was also a case of a malignant tumor of the ileum. There were 4 cases of carcinoma of the caecum.

The percentage of malignancies is about what one would expect considering the average age of this group of people; the incidence of carcinoma is not usually higher in people suffering from pulmonary tuberculosis. In the clinical group there were 4 cases of malignancy. Two of the carcinomata were in the caecum of patients aged thirty-two and forty-six. There was one carcinoma of the stomach in a patient aged forty-eight, and a sixty-seven year old patient had a carcinoma of the liver.

In the group of 102 clinically observed patients who came to autopsy carcinomata were found in 5, 4 of which had been diagnosed clinically as mentioned above. One case had been diagnosed as carcinoma of the stomach because X-ray studies showed a marked deformity, but at autopsy a primary cancer of the liver was found which had pressed on

the stomach to cause the deformity. The 2 cases of carcinoma of the caecum had been readily diagnosed clinically because of the rapid weight loss, persistent blood in the stools and evidence of a palpable mass in the region of the caecum, in accord with the X-ray findings. One carcinoma of the lung had been diagnosed clinically and was verified at autopsy. One case had been diagnosed clinically as a large pelvic tumor but was found at autopsy to be a carcinoma of the ovary.

Diverticula: Diverticula of the gastrointestinal tract were found in most instances only at autopsy. In the nontuberculous lesions of the gastrointestinal tract in the autopsy group, 2 congenital diverticula of the oesophagus were found and one erosion diverticulum. There were 2 gastric and 2 duodenal diverticula. Meckel's diverticulum was present in 9 instances. One diverticulum was found in the caecum, and one in the colon. There were 3 diverticula of the sigmoid.

Amyloidosis: In the autopsy group, amyloidosis appeared in the liver in 162 cases and in the spleen in 214, while in the group of 102 previously studied clinical cases there were 31 cases of amyloidosis of the liver and 38 of the spleen. Clinically, only 6 cases were diagnosed as such In the clinical series, whenever an enlarged liver was found, Congo-red tests were done. These tests, however, were not made routinely in patients suffering from gastrointestinal symptoms, which accounts for the less frequent clinical diagnosis of amyloidosis. As has been pointed out, the gastrointestinal symptoms are apparently exaggerated by the presence of amyloidosis, which may even simulate other gastrointestinal lesions. In 5 of the 102 patients intestinal tuberculosis had been diagnosed, but only amyloidosis was found. In general, as a differential point, it may be suggested that amyloidosis increases vomiting and frequently causes diarrhoea.

Gallbladder lesions: In the 1,000 autopsies, cholecystitis with cholelithiasis was present in 42 instances, while cholecystitis alone occurred in 6 cases. In the 1,000 clinical patients, cholecystitis with cholelithiasis was diagnosed in 6, and cholecystitis alone in 12. Of these 12, 8 had intestinal tuberculosis. There were 4 cases of hydrops of the gallbladder in the clinical series. In the autopsy group, there was one case of hydrops.

The difference between the pathological and the clinical diagnosis of cholecystitis and cholelithiasis is no doubt due to the fact that gallbladder symptoms are absent or masked by the other lesions of the gastrointestinal tract. When the diagnosis of intestinal tuberculosis

is definite clinically, while the gallbladder symptoms might be considered vague, no attempt is made for further X-ray work.

Nontuberculous colitis: In the 1,000 autopsies, there was no reference to nontuberculous ulcerations of the colon, but in the 1,000 clinical patients there were 7 cases of nontuberculous ulcerative colitis as proved by proctoscopic examination, and 27 cases were considered as functional or reflex colitis, nontuberculous in origin. In the 102 autopsies of previously studied clinical cases, there were 2 instances with the clinical diagnosis of functional colitis, and at autopsy the absence of tuberculosis of the intestine was verified.

Appendicitis: In the series of 1,000 autopsies, one gangrenous appendix and one fistula of the appendix were disclosed. One case of congenital absence of the appendix was revealed and 2 appendiceal abscesses.

Nontuberculous appendicitis is extremely difficult to differentiate from the tuberculous caecum or appendix. In our clinical series we diagnosed 11 cases of acute appendicitis, 7 of which had intestinal tuberculosis; 3 as subacute, of which 2 had intestinal tuberculosis; and 22 chronic, of which 16 had intestinal tuberculosis. In the 102 cases studied both clinically and pathologically, the autopsy showed no involvement of the appendix. In a series of this numerical magnitude, we consider ourselves rather fortunate in not having had more perforated appendices, since the appendiceal pains are frequently masked.

Miscellaneous gastrointestinal complications: In the series of autopsies, one case of paralytic ileum was found. Beef tapeworm was found in one case. There were 2 instances of intestinal obstruction of the ileum. There were 2 cases of fistula of the colon, and one of fistula of the sigmoid. The 1,000 patients seen clinically included one case of kidney stones, and 5 cases of peritonitis, 3 of which were tuberculous and 2 nontuberculous. Duodenitis occurred in 5 instances. The group of 102 clinically observed patients disclosed one case of tuberculous peritonitis at autopsy which had been diagnosed as tuberculosis of the bowel.

Amoebiasis: Approximately 75 per cent of the patients in the clinical group had been examined proctoscopically. They all had had routine stool examinations and had been checked for amoebae. About 400 of this group of 1,000 patients had had direct smears made at the time of proctoscopic examination and in no instance had amoebae been found. The literature makes no mention of amoebiasis in pulmonary tuberculosis, and one is led to wonder if amoebae can exist in the presence of an active tuberculosis. When one considers the fact that this study was carried on during an epidemic of amoebiasis in Chicago during the years

of 1933 and 1934, that these patients had been free to leave their institution from time to time, and that they frequently had diarrhoea, but still had never been positive for amoebae, the natural conclusion would be to suppose that amoebiasis cannot exist in the presence of tuberculosis. This problem awaits further study.

Gastritis: In the light of our present knowledge, gastritis occurred in at least 142 of the 1,000 autopsies, or in 14.2 per cent. Of these 142, 84 were chronic superficial, 40 were chronic atrophic, and 18 were chronic hypertrophic gastritis. We have considered those cases chronic superficial gastritis in which the pathologist described "haemorrhages, swollen rugae oedematous in appearance, superficial erosions, and hyperaemic patches;" chronic atrophic gastritis, in which he described a "friable mucosa thinned and grayish in appearance resembling tissue paper, small rugae, and irregular translucent patches;" and chronic hypertrophic gastritis, in which he mentioned "multiple nodules in the body of the stomach separated by fissures, swollen oedematous rugae, and areas of polygonal bosses separated by fine depressions or fine shallow lines." These descriptions compare with those given by Schindler and others, and therefore these cases have been placed in the gastritis group.

For the past year more attention has been directed toward the diagnosis of gastritis in pulmonary tuberculosis by means of gastroscopic examinations which, since November, 1939, are being made routinely, as far as possible. Twenty-eight cases of gastritis have been noted in 60 examinations, of which 16 had intestinal tuberculosis. Gastroscopic studies made during the past six months lead us to believe that gastritis is present in about 40 per cent of patients suffering from gastrointestinal symptoms. A more detailed report of this study will be made at a later date.

The symptoms of nausea, bloating, occasional vomiting and epigastric pain frequently precede more pronounced symptoms so readily diagnosed as intestinal tuberculosis. These early symptoms are highly suggestive of changes in the gastric mucosa. One wonders whether gastritis results from the general debility following intestinal involvement, or whether gastritis, allowing the passage of more viable tubercle bacilli, may be the forerunner of intestinal tuberculosis.

CONCLUSIONS

1. Tuberculous enteritis was diagnosed in 78.3 per cent of 1,000 patients and was found in 71 per cent of 1,000 selected autopsies of patients who had died of pulmonary tuberculosis.

2. Perforation of tuberculous lesions of the gastrointestinal tract has occurred less frequently since the adoption of a smooth, high-vitamin, high-caloric diet.

3. Congenital lesions and benign tumors occur with about the same frequency that one would expect in a comparable series of patients without pulmonary tuberculosis. The same is true of malignancies.

4. The incidence of peptic ulcer in pulmonary tuberculosis is slightly higher than that found in nontuberculous groups.

5. Cholecystitis and cholelithiasis occur with about the same frequency as with any other group of similar ages.

6. Amyloidosis of the liver or the spleen is associated with tuberculosis in about one-third of the cases, and may either exaggerate gastrointestinal symptoms or may simulate other gastrointestinal lesions.

7. Amoebiasis has not been found in any of our patients.

8. Chronic gastritis is a common finding in intestinal tuberculosis, with chronic atrophic gastritis predominating.

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TUBERCULOSIS IN THE RAT[1]

III. The Correlation between the Histological Changes and the Fate of Living Tubercle Bacilli in the Organs of the Albino Rat

C. C. WESSELS

By means of cultural methods, as indicated in the previous paper, multiplication of tubercle bacilli has been shown to occur in the rat after intravenous injection.

Twenty-four hours after infection more human type tubercle bacilli can be cultured from practically all the organs than from rats similarly infected with the bovine microörganisms. Of all the organs, twenty-four hours after infection with both the human and bovine type, the liver contained the largest number of bacilli.

Lurie (1), who used the rabbit and whose method was adopted in these experiments, has shown that at first the human type tubercle bacillus grows more rapidly than the bovine type. Soon, however, a change takes place, causing the destruction of the human bacillus, first in the liver and spleen and later in the lung and kidney. In the experiments of the series here reported, unfortunately, cultures were not made of the human type one week after infection. However, with both the human and bovine types of infection, the destruction first took place in the liver, and after two weeks, when the liver showed definite destruction of bacilli, there was still unabated growth in the spleen and lung.

Confirming the work of Lurie, it was found that two weeks after infection, the destruction of the human type bacillus in all the organs is much more extensive than that of the bovine type bacillus; in the lung no destruction of the bovine type bacillus is observed for two months.

Two months after infection, in case of the human type, the destruction was so marked that the numbers of bacilli were much less in all the organs than twenty-four hours after infection, whereas, in the case of the bovine type, even three months after infection, the number of bacilli in the various organs still exceeded the number of bacilli present in them twenty-four hours after infection. This was found true both with large and small dosage infection.

[1] From the Henry Phipps Institute, University of Pennsylvania, Philadelphia.

In the present experiment an attempt was made to correlate the histopathological changes in the various organs of the albino rat with the numbers of viable bacilli contained in them as indicated by the number of colonies isolated from each organ at various intervals after infection. The purpose was to determine what reactions of the host are concerned with the multiplication and the destruction of the parasite.

The term mononuclear has been used without subdivision into monocyte and clasmatocyte, as employed by Lurie (1). By gradual transition the large mononuclear is transformed into what is designated here as the young epithelioid cell. This is a much larger cell, with abundant foamy or reticulated cytoplasm. The nucleus is usually round and very poor in chromatin. These cells are connected with one another by large processes. They are seen in the early tubercles. Later they become rounded and, as first described by Castren (2), the cytoplasm becomes differentiated into an inner more eosinophilic, more compact, spherical area and a peripheral zone of more basophilic, often vacuolated cytoplasm. It is in this central area that the large accumulation of very finely divided neutral-red granules is seen when the cells are stained supravitally as shown by Lewis (3) and by Sabin and her coworkers (4). This is the mature epithelioid cell.

Another cell playing a part in the tuberculous process in the lung is the alveolar phagocyte, which is a large spherical cell with foamy, abundant, pale staining cytoplasm and an eccentric oval or kidney-shaped vesicular nucleus. Carbon particles and other ingested materials are often found in the cytoplasm. In harmony with the view of Lang (5) and Gardner and Smith (6) that the phagocyte is derived from the so-called septal cell belonging to the general group of connective tissue phagocytes or clasmatocytes, it has been designated here simply as a macrophage.

In these studies various forms of acid-fast material in addition to typical acid-fast rods were noted within the cells. These ranged from ovoid globular, deeply or lightly staining forms of the size of large cocci, or larger, to irregular debris with all the outward characteristics of fragments of acid-fast bacilli, and fine dust-like, scarcely visible, acid-fast particles. The intracellular substance shows a tendency to change in the order given. As to the significance of this material, no agreement has yet been reached by the investigators concerned. There are numerous observations in the literature suggesting that such particles are degeneration products of the tubercle bacillus. Among these are the experiments on "lysis" (7) showing that when tubercle bacilli are

introduced in the tissues or cavities of tuberculous animals, there is a rapid accumulation of acid-fast material and a marked reduction in the numbers of stainable bacilli, associated with heightened resistance of the infected animal to reinfection. In normal animals, similarly treated, intact bacilli persist and granular debris is much less in evidence, but acid-fast material interpreted as degeneration products of the tubercle bacillus has been observed in the cells by numerous workers (8, 9).

An objection that has been urged to this interpretation, even with the reinfected resistant animal, is that when inoculated into guinea pigs this material gives rise to progressive tuberculosis. It has been shown by Lurie (10), however, that the tubercle bacilli of reinfection are in great part destroyed immediately, and that some few bacilli linger in the tissues. These would account for the virulence of such particles. On the other hand Spengler's "splitters" (11), the work of Sweany (12) and especially the single cell studies of Kahn (13) would suggest that the particles seen may be stages in the development cycle of the microorganism. Most recently Lurie (14) has been able to show by *in vivo* studies that tubercle bacilli often multiply by preliminary subdivision into non-acid-fast granules from which the acid-fast rods sprout.

In these studies the occurrence of acid-fast material is correlated with the number of living bacilli cultured. In general it has been found that the bacillus grows more slowly and is destroyed more rapidly in that organ in which more acid-fast material accumulates within a given time.

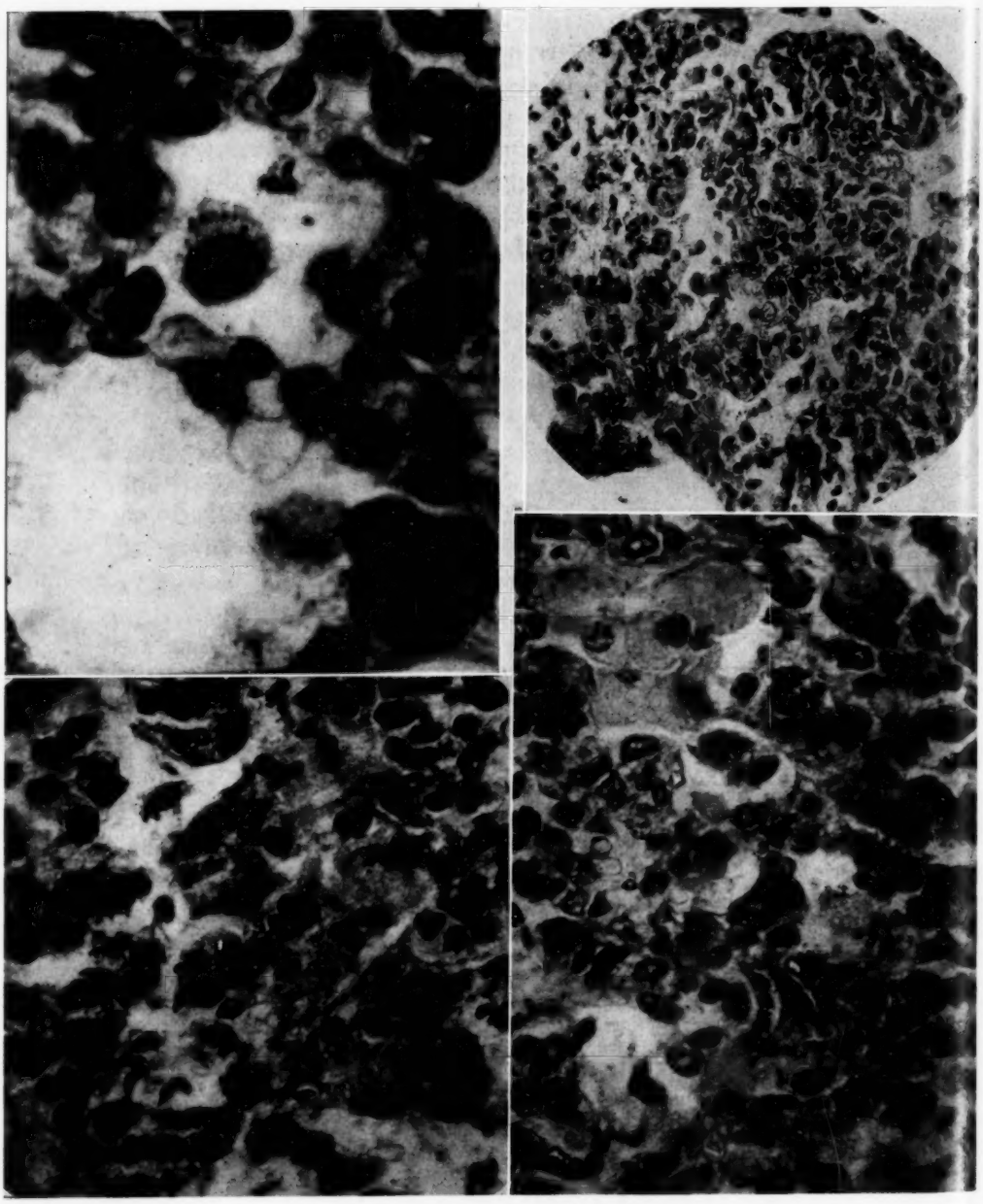
METHOD

The three types of tubercle bacilli, namely, the bovine strain, Ravenel, the human strain, P 15 B, and the avian strain, Avian 12, were used. These have already been described. The dosages and intervals of time when the infected rats were killed have also been given in the previous paper. For histological examination sections were stained with haematoxylin and eosin and by the Ziehl-Neelsen method for tubercle bacilli.

At various intervals equal amounts by weight of suspensions of ground lung, liver, spleen, kidney and tracheobronchial lymph nodes in varying dilutions were seeded upon the surface of Dorset's and modified Loewenstein's egg media, and the number of colonies determined as described in the previous paper.

EXPERIMENTAL OBSERVATIONS

The Lung after Infection with Tubercle Bacilli of Bovine Type: Charts I and III in the previous paper picture the fate of the bovine type tubercle



FIGS. 1–4

bacillus in dosages of 0.1 mg. and 0.001 mg. respectively, when injected intravenously in the albino rat. The histological observations in the lung may be summarized as follows:

From the lung of rat 1 (figure 1) 4,047 colonies were cultured per 10 mg. tissue, twenty-four hours after 0.1 mg. intravenous injection. There were mononuclear accumulations in certain portions of the alveolar septa, in some of which acid-fast particles and bacillary forms could be found. The acid-fast particles suggested the destruction of some bacilli. In rat 8, one week after infection, the infiltrated areas were more numerous and larger than in the previous interval (figure 2). These diffuse infiltrations consisted of a central core of large mononuclears or young epithelioid cells with abundant cytoplasm and vesicular nuclei (figure 3). The cytoplasm was reticulated. Some of these cells contained long bacilli with polar bodies and, often in the same cell, carbon particles were seen. On the periphery of these areas large numbers of mononuclears with hyperchromatic nuclei and little developed cytoplasm were seen, among which mitotic figures could be found. Many carbon-bearing cells were enmeshed by the mononuclears at the periphery of the infiltrations. Almost all the septa of the lung were involved.

EXPLANATION OF PLATES

All microphotographs were made from sections stained either with hematoxylin and eosin or by the Ziehl-Neelsen method.

FIG. 1. Upper Left. Lung of Rat 1, 24 hours after infection with bovine type tubercle bacilli (0.1 mg.); 4,047 colonies were isolated from 10 mg. of tissue. There is an accumulation of mononuclears in the alveolar septa. Acid-fast particles can be seen in some mononuclears. Magnification × 1750; Ziehl-Neelsen stain.

FIG. 2. Upper Right. Lung of Rat 8, 1 week after infection with bovine type tubercle bacilli (0.1 mg.); 251,200 colonies were isolated. There is a general diffuse accumulation of mononuclears almost throughout the septa of the entire lung. Magnification × 340; hematoxylin and eosin stain.

FIG. 3. Lower Left. Lung of Rat 8, 1 week after infection with bovine type tubercle bacilli (0.1 mg.); 251,200 colonies were isolated. The infiltration consists of a central core of large mononuclears or young epithelioid cells with abundant cytoplasm and vesicular nuclei, surrounded by mononuclears with hyperchromatic nuclei and little-developed cytoplasm. Bacilli, as well as a few carbon particles, can be seen. Magnification × 730; Ziehl-Neelsen stain.

FIG. 4. Lower Right. Lung of Rat 3, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 485,000 colonies were isolated. The lesion is of a combined interstitial and alveolar character. Lying apparently within what remains of the alveolar cavity are cells with a large amount of highly vacuolated cytoplasm (foamy). Transitional stages between vacuolated cells and mononuclears can be seen in the alveolar septa. A few carbon particles can be seen in the highly vacuolated cells. Magnification × 730; Ziehl-Neelsen stain.

In addition there was hypertrophy of the intrapulmonary lymph follicles. The bacilli were more numerous within the cells than twenty-four hours after infection. This was confirmed by culture, suggesting the multiplication of the bacilli within the macrophages. The simultaneous occurrence of acid-fast material in the same cells suggested that destruction of bacilli was also taking place.

The microörganisms had greatly increased in number by the end of the second week; the lung of rat 3 revealed a characteristic picture (figure 4). There was hypertrophy of the intrapulmonary lymph follicles, and, within these, nests of young epithelioid cells were found. There was no exudation into the alveoli. There was a wide-spread thickening of the alveolar septa, but this was less diffuse than in the previous interval. Among these infiltrations were found numerous ill defined nodules. These were of a combined interstitial and intraälveolar character. They were composed of alveolar septa which had been greatly thickened by the accumulation of mononuclear cells. Lying apparently within what remained of the alveolar cavity, were numerous large polygonal cells with much cytoplasm, which was highly vacuolated and faintly eosinophilic. In the regions of septal thickenings, these large foamy cells were less frequent. Transitional cells between vacuolated cells and the mononuclears could be seen in the alveolar septa. Isolated tubercle bacilli and carbon particles could also be seen within these large, coarsely vacuolated cells. In the neighborhood of these inflammatory foci the lining alveolar cells were at times transformed into cuboidal and columnar forms.

In the lung of rat 9, two weeks after infection, the picture was fundamentally the same as in rat 3 except that the large vacuolated cells were less frequent. In their place were occasionally found rounded cells with uniformly distributed finer vacuoles, resembling more closely the epithelioid cell as found in the rabbit. These cells, as well as the large foamy cells described above, often contained carbon particles. Mitotic figures could still be seen. The investing collar of mononuclears was less prominent than in the one-week interval. Their place was taken by young epithelioid cells. In some lesions bacilli were found in the so-called young epithelioid cells which were in the transitional stages between mononuclears and the large foamy cells. These transitional cells also contained carbon particles and, in places where bacilli occurred, the organism appeared to be in the vacuoles. Bacilli could not be found

in the vacuolated round cells. It is noteworthy that much fewer tubercle bacilli were isolated from this rat than from rat 3, in which the large foamy cells were more prominent.

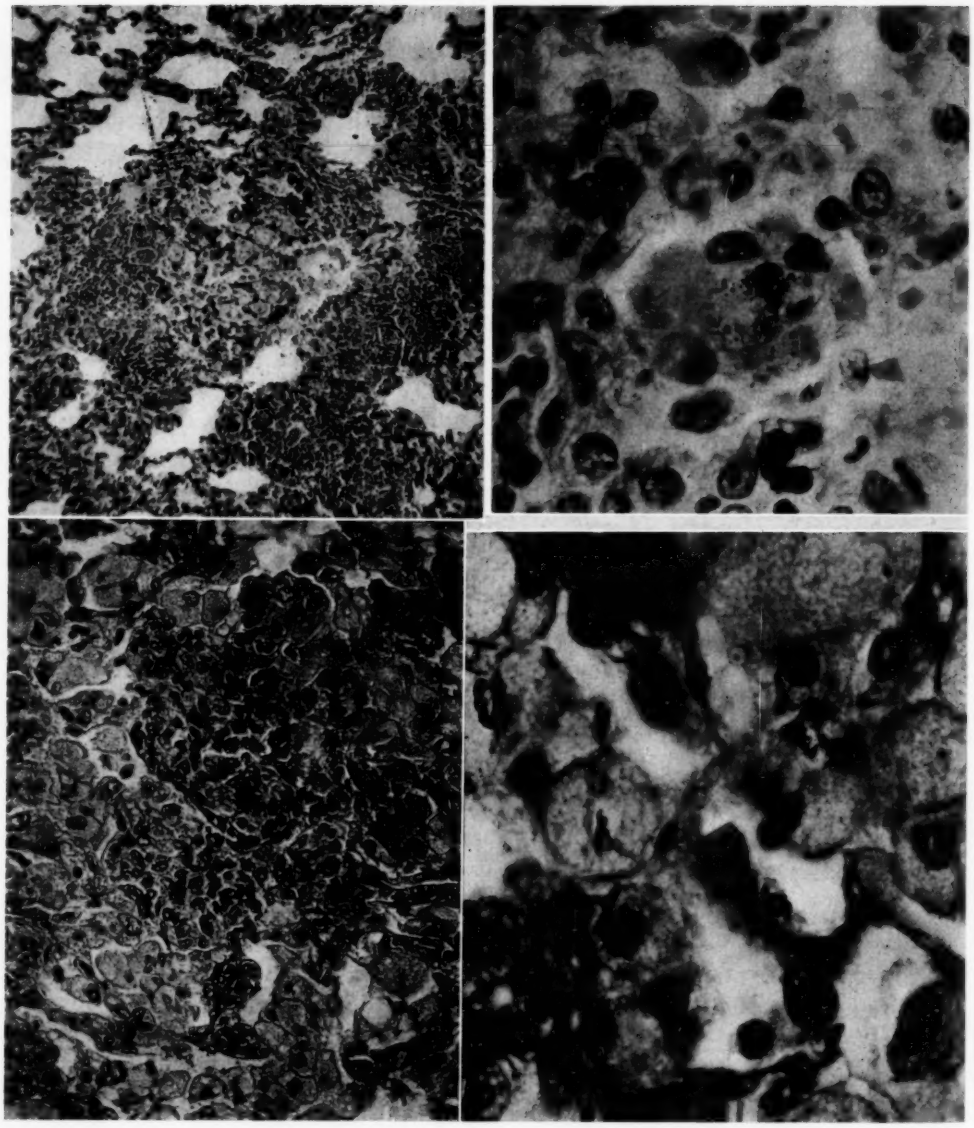
One month after infection in rat 4, the lesion (figure 5) was observed from which the greatest number of viable bacilli were recovered (1,023-000 colonies per 10 mg. tissue). Large sections of parenchyma were replaced by diffuse tuberculous tissue. The chief difference between this and the previous interval was in the number and prominence of the foamy cells, these now being more numerous. Transition forms also could readily be seen. Many of the foamy cells, as well as transitional types, were apparently lying free in the alveoli. Bacilli were most easily found in large numbers in the transitional types (figure 6). The numbers found accorded well with the cultural findings. Many of the foamy cells contained carbon particles. The foamy cell had a peripheral zone which was denser and more basophilic. Bacilli were more easily found in those foamy cells in which part of the cytoplasm was still in the transitional stage.

In rat 10, at the same interval as rat 4, the picture of the lesion was essentially the same as above, except that here the foamy cells were more numerous and larger. The vacuoles in the latter coalesced to form big irregular spaces. In addition, some of the foamy cells showed vesicular nuclei, some, only remnants of nuclei and others, total disappearance of the nucleus.

The typical lesion, as well illustrated here (figures 6 and 7), was constituted as follows: Foci of lightly staining foamy cells were surrounded by young epithelioid cells and transitional forms containing bacilli and carbon particles. In the central zone some of the foamy cells had lost their nuclei and the vacuoles had coalesced into large and irregular spaces, still containing the tell-tale carbon particles, proving their origin.

Two months after infection, the lesion was more advanced. The foamy cells were more abundant and numerous. The bacilli were much less in evidence and still within young epithelioid cells. Some of the foamy cells had definitely degenerated and were broken up, while the nuclei had disappeared. In some of the bronchi collections of these degenerated foamy cells could be seen.

Three months after infection the foamy cells in lesions of rat 6 were more numerous than in the previous interval. Most of the foamy cells



FIGS. 5–8

FIG. 5. Upper Left. Lung of Rat 4, 1 month after infection with bovine type tubercle bacilli (0.1 mg.); 1,023,000 colonies were isolated. A large part of the parenchyma is replaced by diffuse tuberculous tissue. Many of the foamy cells as well as the transitional types are apparently lying free in the alveoli. Magnification × 80; hematoxylin and eosin stain.

FIG. 6. Upper Right. Lung of Rat 10, 1 month after infection with bovine type tubercle

had become disintegrated and the lesions were regressing. Some of the alveoli were filled with the disintegrated foamy cells. The bacilli were very few and only in foci where there were young epithelioid cells.

In rat 12 of the same interval the lesion was like that of rat 6, except that the regressive changes were more marked (figure 8). Most of the pulmonary tissue consisted of large foamy cells, some of which were in various stages of degeneration. In some of the transitional forms many acid-fast granules and carbon particles could be found, but bacilli were demonstrable with difficulty.

The Lung after Infection with Tubercle Bacilli of Human Type: Charts II and IV picture the fate of the human type of tubercle bacillus in dosages of 0.1 mg. and 0.001 mg. respectively, when injected intravenously in the albino rat.

Two weeks after inoculation, in bovine infection there were 382,550 colonies, as compared to 189,900 colonies in the disease caused by the human type bacillus. As was already shown, twenty-four hours after injection almost three times as many colonies were isolated from rats infected with the human than from rats infected with the bovine type. It is, therefore, reasonable to assume that either the destruction of the human type is more effective or that the growth of this organism is more restricted than that of the bovine type. Histological evidence suggests more rapid destruction (figure 9). In general the changes were the same as with the bovine type, except that in the human infection the whole process was more mature and the lesions further advanced. There were more foamy cells and more broken down bacilli. In the bovine infection, two months after infection it will be noted that there was still no

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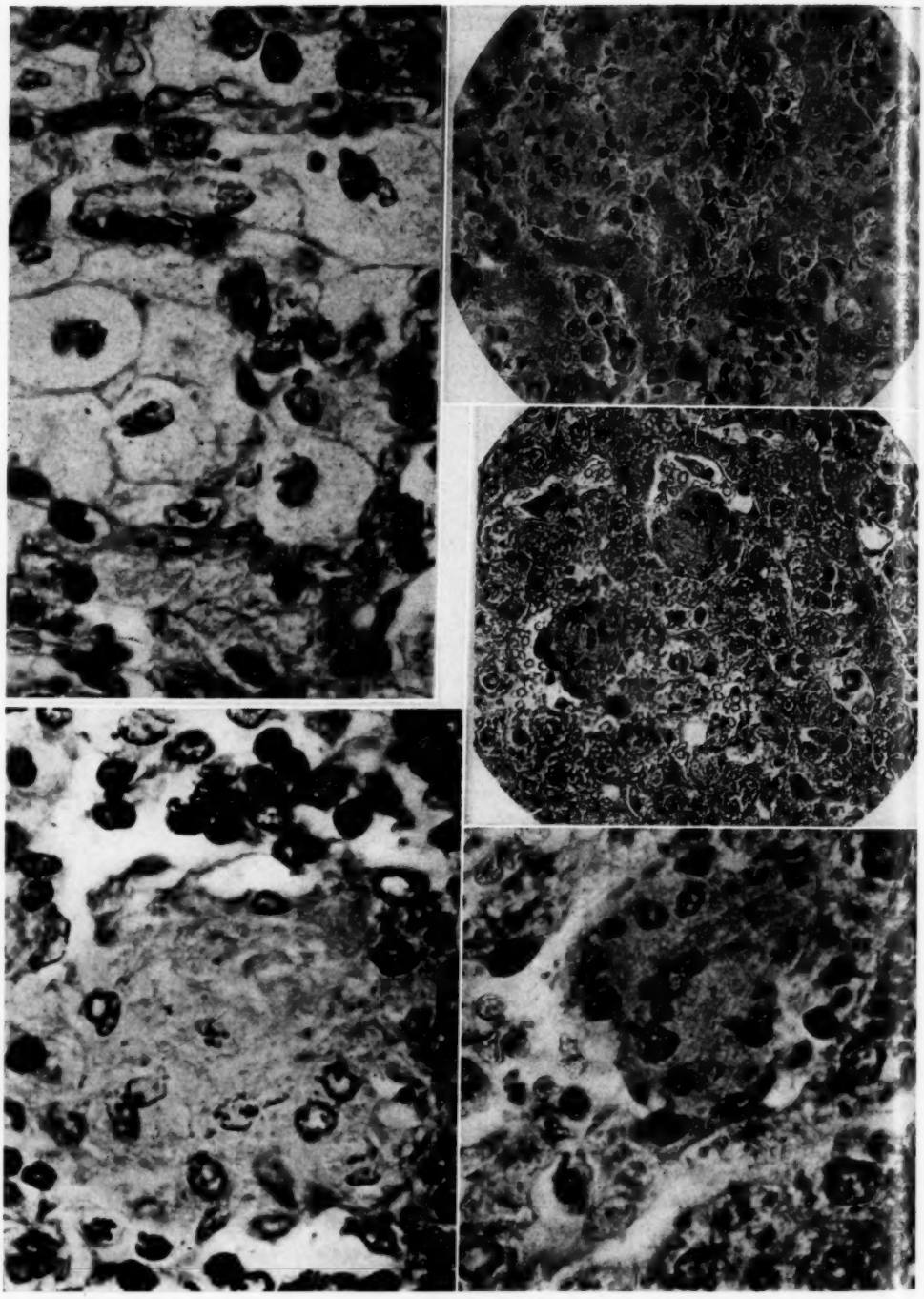
bacilli (0.1 mg.); 420,000 colonies were isolated. The picture is essentially the same as in Rat 4, except that here the foamy cells are more advanced, as can be seen from the large vacuoles, and show coalescent cytoplasm and loss of nuclei in some of the cells. Bacilli, acid-fast granules and carbon particles can be seen in young epithelioid cells at the periphery of the nodules. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 7. Lower Left. Lung of Rat 10, 1 month after infection with bovine type tubercle bacilli (0.1 mg.); 420,000 colonies were isolated. The typical lesion is well illustrated here; it consists of strands of young epithelioid cells with reticulated cytoplasm. Interspersed between these, there are lighter zones consisting of foamy cells with large, uniform, regular vacuoles. Some of the foamy cells have lost their nuclei. Magnification × 340; hematoxylin and eosin stain.

FIG. 8. Lower Right. Lung of Rat 12, 3 months after infection with bovine type tubercle bacilli (0.1 mg.); 71,000 colonies were isolated. There are marked regressive changes and most of the pulmonary tissue consists of large foamy cells, some of which contain tubercle bacilli. A number of the cells are undergoing degeneration. Magnification × 1000; hematoxylin and eosin stain.



FIGS. 9–13

destruction of bacilli, 715,000 colonies being isolated as compared to 7,800 colonies in the human type. This accords very well with the associated histological changes. In the human infection the whole process was not only more mature, but the regressive changes, especially of the foamy cells, were more prominent.

No additional significant information was obtained from correlating the histological changes with the fate of bovine or human bacilli in smaller dosage.

In summary, therefore, it may be stated that the tubercle bacillus of whatever type initiates the multiplication of the mononuclear cells. The bacilli multiply within their substance and the cells hypertrophy, their cytoplasm becomes reticulated, their nuclei vesicular and they assume the shape of what has been designated here as the young epithelioid cells. Gradually, acid-fast particles accumulate within their substance, culturally the bacilli slowly diminish in their growth, and associated with these changes in the fate of the microörganism, the young epithelioid cells enlarge still more. They become rounded and their cytoplasm becomes highly vacuolated, assuming the character of the foamy cell.

FIG. 9. Upper Left. Lung of Rat 26, 2 weeks after infection with human type tubercle bacilli (0.1 mg.); 189,900 colonies were isolated. The picture here is the same as with the bovine large dosage infection except that here the whole process is more mature and the lesions are further advanced, as can be judged from the more numerous typical foamy cells. Magnification × 1000; hematoxylin and eosin stain.

FIG. 10. Upper Right. Liver of Rat 2, 1 week after infection with bovine type tubercle bacilli (0.1 mg.); 94,300 colonies were isolated. In the sinuses there are diffuse collections of large mononuclears with varying amounts of cytoplasm and nuclei in different degrees of vesicularity. Magnification × 340; hematoxylin and eosin stain.

FIG. 11. Center Right. Liver of Rat 3, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 15,682 colonies were isolated. There are localized nodules of more mature epithelioid cells, with more abundant compact and homogeneous cytoplasm than is seen in Rat 2, Figure 10. Magnification × 340; hematoxylin and eosin stain.

FIG. 12. Lower Left. Liver of Rat 9, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 67,100 colonies were isolated. The bacilli are still accumulating. The young epithelioid cells have abundant, spongy, reticulated cytoplasm containing tubercle bacilli; the vacuoles are large and irregular. The nodule is surrounded by numerous actively-growing mononuclears with hyperchromatic nuclei and sparse cytoplasm. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 13. Lower Right. Liver of Rat 26, 2 weeks after infection with human type tubercle bacilli (0.1 mg.); 3,866 colonies were isolated. Marked destruction of the bacilli has taken place. The nodule is composed of a syncytium of mature epithelioid cells with compact homogeneous cytoplasm and minute, barely visible, uniform vacuoles. There is no collar of growing mononuclears about the focus; it lies in juxtaposition to the parenchyma. Magnification × 1000; Ziehl-Neelsen stain.

These rarely contain any bacilli, although carbon particles can still be found in them. The human type tubercle bacilli are more rapidly destroyed in the lung of the rat than the bovine type. Foamy cells appear earlier in the human infection.

It is noteworthy that avian type bacilli scarcely multiply in the lung of the rat and little evidence of their destruction occurs. Hence, foamy cells are inconspicuous in the lung of rats infected with avian type bacilli.

The process in the lung is largely diffuse. No typical nodular tubercles are formed. Caseation does not take place. The secondary polymorphonuclear infiltration preceding caseation in the susceptible animal is therefore not encountered in the rat, nor does softening occur. It is noteworthy that only slight and atypical tuberculin sensitivity develops in the rat.

Instead of the development of caseation, the foamy cells gradually disintegrate by the coalescence of the vacuoles and the disruption of the nuclei until nothing but shreds are left of the foamy cells, which are absorbed (see figure 22).

The Liver after Infection with Tubercle Bacilli of Mammalian and Avian Types: Despite the localization of larger numbers of bacilli in the liver than in the lung, the initial inflammation is very much less in the liver. The Kupffer cells show slight enlargement; occasional polymorphonuclears are encountered and a few isolated bacilli lying free between the liver cells are detected, but only with the big dosage of bovine and avian type bacilli.

In rat 2, one week after infection with the big dosage of bovine type, yielding the greatest number of colonies (94,300), the following observations are significant. Many of the Kupffer cells were swollen throughout the liver. In the sinuses there were collections of large mononuclears of varying size. The nuclei of these were in varying degrees of vesicularity and their cytoplasm was more or less developed. Some of the cells consisted of mononuclears with dense nuclei and a small amount of cytoplasm. In others the nuclei were more vesicular and the cytoplasm was more abundant. In still others the cells had assumed the structure of young epithelioid type cells. The lesion was diffuse. Mitotic figures in the Kupffer cells were noted (figure 10).

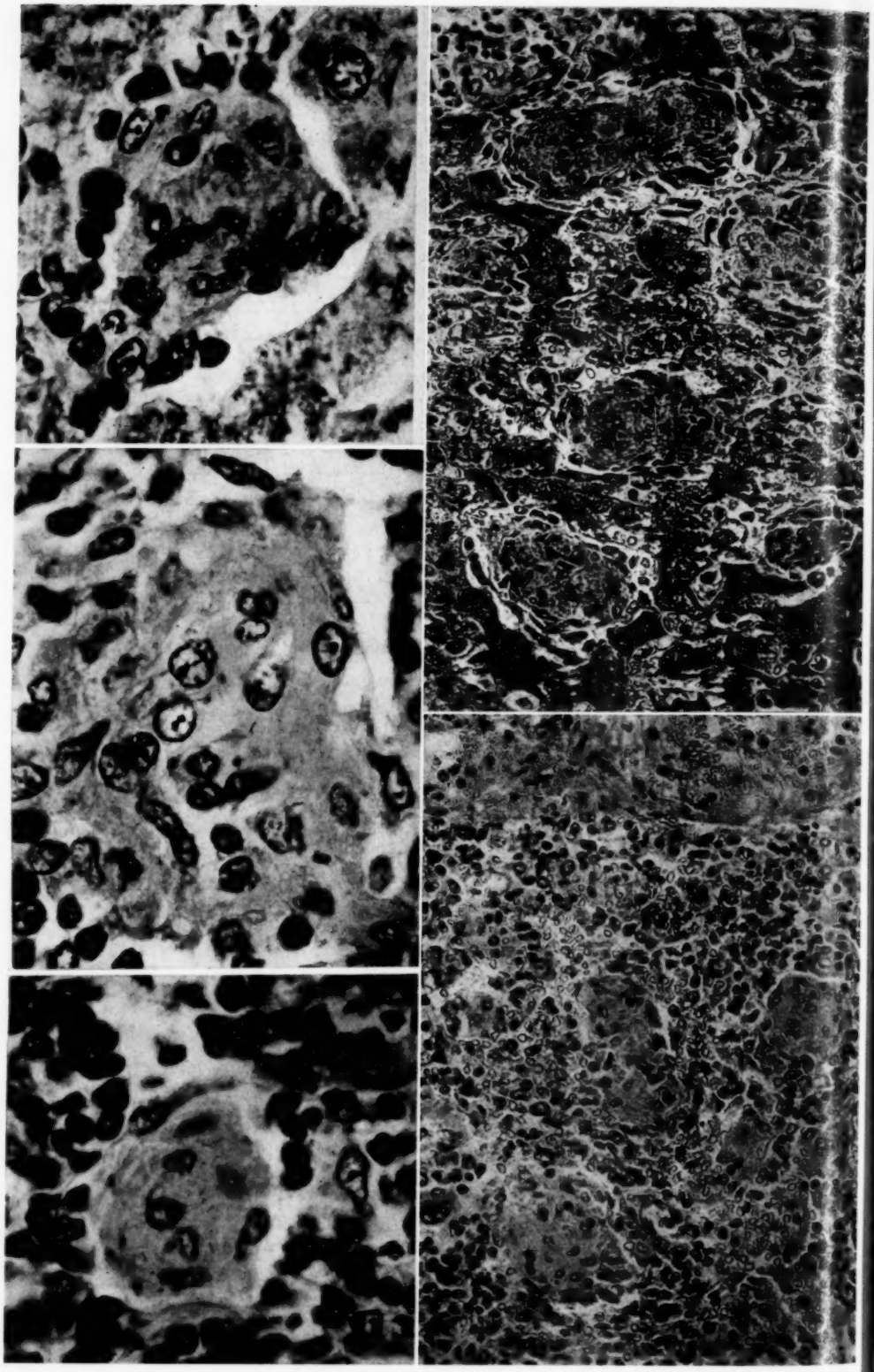
From the liver of rat 3, 15,682 colonies were isolated two weeks after infection, a marked reduction in the number of microörganisms as compared with those obtained from rat 2 of the previous week. The

essential differences in the lesions of these two rats may be summarized as follows. In rat 3 the intrasinusoidal cellular collections were localized. They were diffuse in rat 2. Mitotic figures were absent in rat 3. They were numerous in rat 2. The cytoplasm of the mononuclears in the first week was reticulated and the vacuoles were large and irregular. In the second week the vacuoles were more uniform and smaller. The epithelioid cells were more mature, with more compact and homogeneous cytoplasm (compare figures 10 and 11).

Figures 12 and 13 illustrate the essential points in the correlation between the fate of the bacilli and the host response. In the former is shown a nodule in the liver of rat 9 two weeks after infection with 0.1 mg. of bovine type bacilli. The multiplication of the bacilli was still continuing, 67,100 colonies having been cultured from this liver. The cytoplasm of the young epithelioid cells was very abundant, spongy and reticulated. The vacuoles were large and irregular. The nodule was surrounded by numerous actively growing mononuclears with hyperchromatic nuclei and little developed cytoplasm. Figure 13 shows a similar nodule in the liver of rat 26, also two weeks after infection with the same dose, but with the human type bacillus. Here not only had growth ceased, but marked destruction had taken place. Only 3,866 colonies were cultured, as compared with 20,470 obtained from a rat simultaneously injected with the same suspension of bacilli, but killed twenty-four hours after infection. The nodule was composed of a syncytium of mature epithelioid cells with compact homogeneous cytoplasm and minute uniform vacuoles. The nodule was not surrounded by any growing mononuclears but lay in juxtaposition to the parenchymatous liver cells.

Thus it is clearly seen that with the transformation of the young into the mature epithelioid cell in the rat's liver, there is a marked destruction of bacilli. At the same time the mononuclears in the vicinity of the nodule cease growing and accumulating about the focus. Since the human type of tubercle bacillus is more rapidly destroyed than the bovine type bacillus, mature epithelioid cell formation takes place more quickly in human infection. The foamy cells with their large vacuoles as seen in the lung are not encountered in the liver of rats infected with mammalian bacilli. Correspondingly, the destruction of bacilli in the liver is very much more effective with both human and bovine type bacilli.

While destruction of the bacilli, even of the bovine type, sets in with



FIGS. 14–18

marked intensity as early as the second week after infection, the bacilli persist in large numbers even as late as three months after infection. They are found in large numbers as typical acid-fast rods and as beaded forms within mature epithelioid cells which have frequently fused to form foreign body giant cells (figure 14). In some of these, the epithelioid cells are apparently disintegrating, as suggested by the fragmentation of the cytoplasm into shreds and the formation of empty spaces. The nuclei, however, remain intact. At no time were any signs of necrosis or caseation found, despite the fact that numerous tubercle bacilli were demonstrable in the cells. There appears to be a disproportion between the number of bacilli cultured and those demonstrable microscopically. It is possible that many of the latter were dead.

Few observations have been made with the avian infection. Figure 15 illustrates the wide-spread nodular lesions in the liver of a rat two weeks after such an infection, as well as the diffuse infiltration of the sinusoids by numerous mononuclears. While the bacilli in this liver had not decreased in number as compared with those cultured twenty-four hours after infection, the bacilli cultured at this time following a bovine infection showed a tenfold increment over the original deposition. Yet the lesion in the latter was much less extensive. The significance of this observation is problematical. Whether the more effective dispersion of the avian type bacillus in the inoculum determines a more wide-spread seeding of the microörganism and hence a more pervasive lesion has not been determined. It is well known that avian type tuber-

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FIG. 14. Upper Left. Liver of Rat 5, 2 months after infection with bovine type tubercle bacilli (0.1 mg.); 3,540 colonies were isolated. A foreign body giant cell is seen containing tubercle bacilli and acid-fast particles. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 15. Upper Right. Liver of Rat 32, 2 weeks after infection with avian type tubercle bacilli (0.1 mg.); 28,890 colonies were isolated. The culture shows no destruction of the bacilli; hence the diffuse and wide-spread lesions in various stages as can be judged from the cytoplasm. Magnification × 340; hematoxylin and eosin stain.

FIG. 16. Lower Right. Spleen of Rat 3, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 80,570 colonies were isolated. The splenic pulp is more affected than the corpuscles; the lesions are wide-spread. Magnification × 360; hematoxylin and eosin stain.

FIG. 17. Center Left. Spleen of Rat 9, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 130,500 colonies were isolated. The nodules are not discrete. The cytoplasm is reticulated and spongy, and bacilli can be found within them. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 18. Lower Left. Spleen of Rat 4, 1 month after infection with bovine type tubercle bacilli (0.1 mg.); 5,000 colonies were isolated. This nodule is more mature than the lesions in Rat 9. Note the homogeneous cytoplasm of the epithelioid cells as compared to Fig. 17. Many bacilli are present. Magnification × 1000; Ziehl-Neelsen stain.

cle bacilli can be much more easily dispersed into isolated rods than mammalian bacilli. This is clearly seen in the observation that much larger numbers of tubercle bacilli were cultured from all the organs twenty-four hours after an avian than after a similar bovine or human inoculation.

Spleen: A correlation between the fate of the bacilli and the host responses in the spleen reveals essentially the same relations as described for the liver. It is noteworthy that tubercle formation is much more wide-spread in the pulp than in the corpuscles (figure 16). As was found in the liver, so also in the spleen, late in the course of the disease, many more tubercle bacilli were demonstrable histologically than one would expect from the number of bacilli cultured. Thus in the spleen of rat 9 (figure 17), two weeks after infection, with 130,500 colonies per 10 mg. of tissue, only a few bacilli could be seen in the spongy reticulated cytoplasm of the young epithelioid cells. Two weeks later in rat 4 (figure 18), with only 5,000 colonies from the same amount of tissue, numerous bacilli and acid-fast particles could be seen within the compact, almost homogeneous cytoplasm of the mature epithelioid cells. Whether the bacilli here were all mature and hence all acid-fast, or whether the bacilli at this time were dead and disintegrating, as suggested by the acid-fast particles, cannot be stated. It is possible that in the earlier stages of the infection, when active multiplication of the microörganism is taking place (14), many bacilli are in a non-acid-fast state, hence the disproportionately small numbers of visible bacilli.

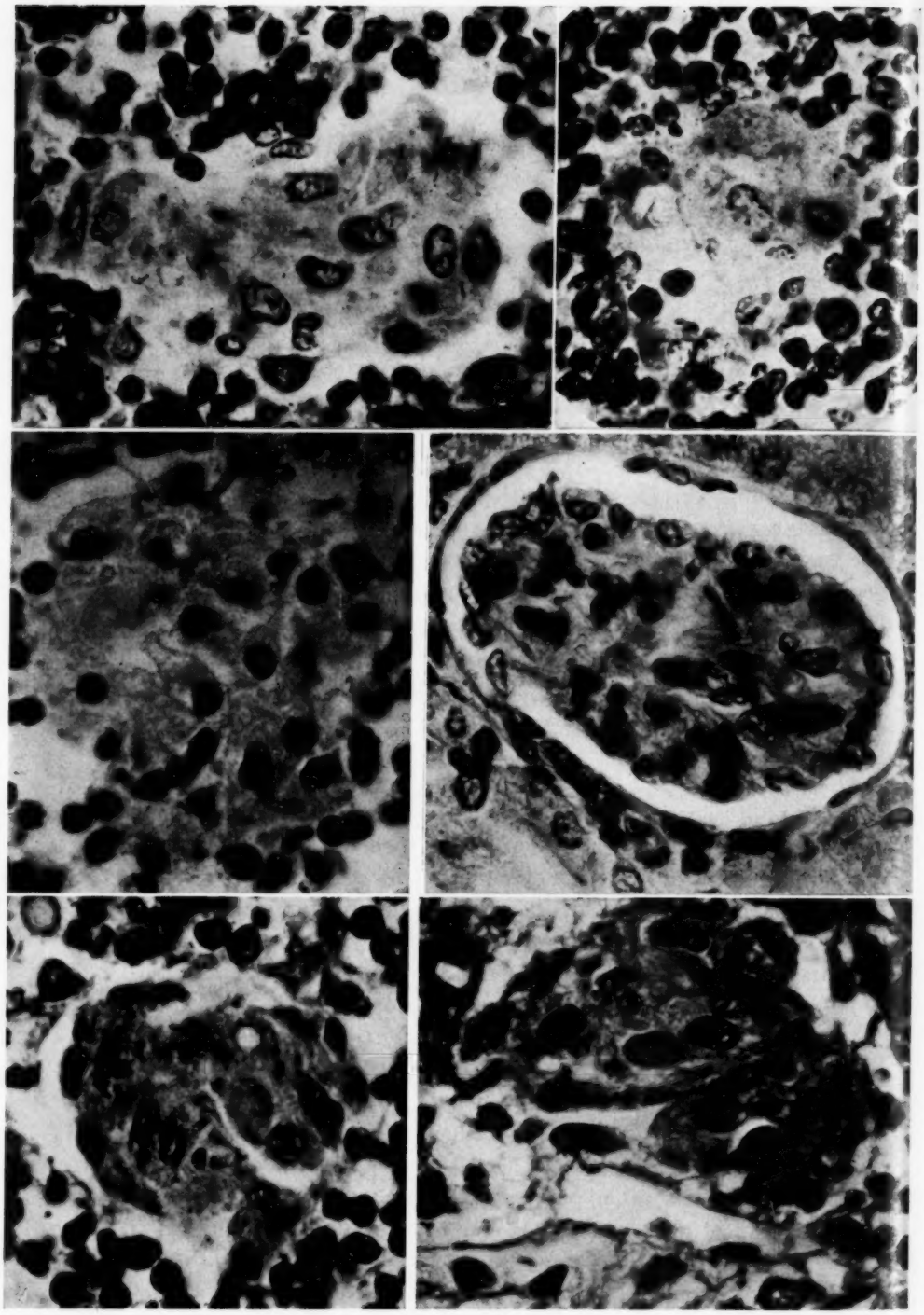
As was found in the liver, large numbers of tubercle bacilli persisted in the spleen, especially in the case of the bovine type, even three months after infection. The bacilli seemed to live in symbiosis with the tissues, for at no time was there evidence of any injury to the tissues as a result of the presence of living tubercle bacilli.

Tracheobronchial Lymph Nodes: As seen in the charts accompanying the previous paper, the fate of the bacilli in the tracheobronchial lymph nodes runs a course closely parallel to that of the microörganism in the corresponding lung which it drains. This holds for each strain and dose. The only exception to this rule was found in the tracheobronchial lymph node of a single rat cultured two months after an inoculation of 0.001 mg. of avian bacilli. It is questionable whether this isolated observation has any particular significance. This would suggest that most of the changes in the tracheobronchial lymph nodes result from bacilli and cells originating in the lung and overflowing into the drainage

lymph nodes. It is not surprising, therefore, that the foamy cells described in the lung are also encountered in these lymph nodes. Figures 19 and 20 illustrate these cells. It is noteworthy that while these epithelioid cells have rounded, more or less uniform vacuoles, resembling the foamy cells of the lung, these are definitely smaller and the vacuoles are not quite as prominent as those in the lung. It is probable that the difference is due to the different environment in which these cells find themselves when they localize in the tracheobronchial lymph nodes, rather than to inherent differences in their properties. As was noted above with the spleen and liver, so here also, late in the course of the disease, many more tubercle bacilli were visible than could be accounted for by the cultural observations. The same explanation applies here as was given above in detail for the liver and spleen. Again no necrosis or caseation was noted, but the cytoplasm of the epithelioid cells had become fragmented into shreds (figure 22). Often the cytoplasm of these epithelioid cells retained the fuchsin stain after treatment with hydrochloric acid (figure 21). Again large numbers of viable tubercle bacilli remained in the lymph nodes, as in the case of rat 6, three months after inoculation of 0.1 mg. of bovine bacilli, where 7,660 colonies were cultivated, apparently living in symbiosis with the tissues without injuring the latter.

Kidney: As may be seen in the charts, there was no consistent trend toward multiplication of the bacilli in the rat's kidney. In all instances, except with large dosage bovine infection, the bacilli gradually diminished and then persisted in insignificant numbers for three months. These bacilli may well have been derived from microörganisms circulating in the blood, emanating from lesions elsewhere in the body. In the kidneys of rats infected with the large dose of bovine tubercle bacilli, occasional foci of intertubular and periglomerular mononuclear infiltrations were encountered in the second week after infection, as seen in figure 23. Later rare, minute, medullary intertubular epithelioid cell tubercles were found (figure 24). These changes corresponded with the slight waves of multiplication and destruction noted in these instances.

Relation between Histological and Cultural Demonstration of Bacilli: Although there is some parallelism between the number of tubercle bacilli demonstrable histologically and the number of colonies that can be isolated from a given tissue, yet, as has been stated by Lurie (1), the culture method is far more efficient in indicating quantitative relations. In some instances, twenty-four hours after infection, in spite of very



FIGS. 19–24

large numbers of bacilli isolated from an organ, histologically none or very few could be demonstrated. It is possible that early in the course of the disease the bacilli are in a non-acid-fast state as shown by Kahn (13) and Lurie (14). Later, however, with the maturation of the tubercle, the parallelism is much closer, but, at times, histologically the bacilli were in such large numbers as to be out of accord with the cultural findings which showed few colonies. In these cases it is permissible to conclude that most of the bacilli were no longer viable.

As early as twenty-four hours after infection, acid-fast material could be detected in the mononuclears, a fact which may be indicative of destruction of bacilli. On the other hand, when it was shown culturally that definite destruction of the bacilli had taken place, histologically very little or no acid-fast material could be found.

With the mammalian and avian types, although the primary deposition of the bacilli in the liver was greater than in the lung, the initial inflammatory reaction was more intense in the lung. The reaction in each organ with the less virulent human type was less pronounced than with the bovine type.

Lurie (1) has shown that individual resistance is linked with the ability to form mature tubercles early. The findings were the same in

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FIG. 19. Upper Left. Tracheobronchial lymph node of Rat 5, 3 months after infection with bovine type tubercle bacilli (0.1 mg.); 800 colonies were isolated. The cytoplasm of the epithelioid cells assumes a vacuolated foamy appearance. The bacilli are numerous and in all shapes. They appear as long, beaded and granular forms, or like chains of dust particles. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 20. Center Left. Tracheobronchial lymph node of Rat 27, 2 months after infection with human type tubercle bacilli (0.1 mg.); 430 colonies were isolated. The epithelioid cells show a foamy cytoplasm. Bacilli can be seen within the epithelioid cells. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 21. Lower Left. Tracheobronchial lymph node of Rat 17, 2 months after infection with bovine type tubercle bacilli (0.001 mg.); 1,190 colonies were isolated. The cytoplasm of the epithelioid cells retains the fuchsin stain, suggested in this photograph by its dark color. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 22. Upper Right. Tracheobronchial lymph node of Rat 30, 2 months after infection with human type tubercle bacilli (0.001 mg.); 200 colonies were isolated. Note the fragmentation of the cytoplasm of the regressive epithelioid cells. Magnification × 1000; Ziehl-Neelsen stain.

FIG. 23. Center Right. Kidney of Rat 3, 2 weeks after infection with bovine type tubercle bacilli (0.1 mg.); 2,573 colonies were isolated. There is a slight infiltration of mononuclears around the glomerulus. Magnification × 1000; hematoxylin and eosin stain.

FIG. 24. Lower Right. Kidney of Rat 6, 3 months after infection with bovine type tubercle bacilli (0.1 mg.); 1,011 colonies were isolated. A medullary nodule shows one bacillus within the cytoplasm. Magnification × 1000; Ziehl-Neelsen stain.

these experiments. It is shown in instances where rats were simultaneously infected with the same strain and killed at the same time, that destruction or retardation of the bacilli is greater in animals in which maturation of the tubercle and epithelioid cells has proceeded further.

From the varying fate of the bacilli in the different organs it is apparent that the mononuclears of the several organs have a varying capacity for destruction of the bacilli, and these experiments confirm the findings of Lurie (1) in that the transformation of the mononuclears into mature epithelioid cells follows the destruction of the bacilli.

DISCUSSION

From these experiments it is clear that in tuberculosis of the rat the mononuclear is the cell which plays the most important rôle in combating the disease.

Lurie (1), in his studies on the susceptible animal, has proved that after infection, concurrent with the multiplication of bacilli, the mononuclears accumulate by mitosis and develop in maturity until the epithelioid cell stage is reached which forms the tubercle. The epithelioid cells are concerned with the destruction of the bacilli, and when destruction or retardation in the growth of the bacilli sets in, there is cessation of mitosis and giant cells make their appearance. In the resistant animal, the rat, although the general trend is the same, there is a great difference in the development and ultimate fate of the mononuclears, as indicated in the foregoing pages. From the experiments recorded, it is evident that the growth of the bacillus is associated with the multiplication of mononuclears and the transformation of the latter into mature epithelioid cells, related, in turn, with the destruction of the bacillus.

Lurie (1) has found that in the rabbit the appearance of giant cells is associated with cessation of mononuclear regeneration by mitosis and is coincident with cessation of multiplication or marked reduction in the number of living bacilli. In these experiments on the rat, Langhans giant cells were not observed, but foreign body giant cells were frequently encountered.

Caseation is one of the outstanding phenomena of tuberculosis in the susceptible animal. In the rat, however, although in general the cellular response of the host to the invading parasite is much the same, at no time is there necrosis of the cells. It is, therefore, possible that the native immunity of the rat is at least in part due to the failure of the development of cell necrosis or caseation. For in the susceptible animal

caseous tissue eventually undergoes softening, which determines the fatal issue, even in chronic tuberculosis.

To what is the necrosis of the cells due, and why is the phenomenon not encountered in the rat, even after three months' infection with virulent bovine tubercle bacilli, when as many as 110,000 colonies were cultured from 10 mg. of pulmonary tissue?

It has been shown by Seibert (15) that specific anaphylactic sensitization can be produced in normal rabbits and guinea pigs by repeated injections of highly purified, undenatured protein of tuberculin. This sensitization is of a high degree. It has been shown by Rich and Lewis (16) in tissue culture studies that tuberculin has a toxic action on explants of tuberculous tissue. These observations have been extended by Aronson (17). Moen (18) has produced evidence showing that this sensitivity of the cells is retained by them after several generations *in vitro*.

In the experiments of the investigation here reported, where normal rats were sensitized with the same undenatured protein of tuberculin, the typical reaction (Arthus phenomenon) as seen in the rabbit or guinea pig could not be produced. Further, in tuberculous rats the typical tuberculin reaction as seen in rabbits and guinea pigs was not evident.

These observations, therefore, suggest that the rat cannot become sensitized to the tubercle bacillus or its protein derivatives to the same extent or in the same manner as is true of the susceptible rabbit or guinea pig.

Seibert (19) in her studies on the effect of anaphylactic sensitization with tuberculin protein upon the development and course of experimental tuberculosis has come to the conclusion that this type of hypersensitiveness to tuberculin protein confers no immunity or increased resistance to subsequent tuberculous infection. On the contrary it seems to hasten and extend the lesion and to be associated with much more extensive necrosis and caseation than is found in unsensitized animals.

Maximow (20), in his tissue culture experiments with rabbit cells, has shown that individual bacilli tend to enter wandering cells. The entrance of the bacilli, as pointed out by Long (21), may not be due to phagocytic action alone, but also to physicochemical conditions. The experiments of the Mudds (22) on the surface properties of tubercle bacilli support this suggestion. These workers showed that acid-fast

bacilli lying at the interface of water and oil are drawn into the latter. It is, therefore, quite possible that the outer lipoid or lipoid-protein film in living cells behaves as do the fat globules in these experiments. The drawings of Maximow show that, after entrance into the growing cells, the bacilli multiply. Further, these cells not only increase in size but also undergo mitosis at a more rapid rate than in uninfected cultures. Furthermore, cells remote from the bacilli also showed the signs of stimulation suggesting that a soluble product of the bacillus might be responsible for the effect. Chemotaxis towards the growing colonies of bacilli was apparent in the active motion of the cells in that direction. He even noted signs of beginning necrosis, reminding him of caseation. He also found evidence of bacillary destruction in some of the cells. Some of Maximow's strains tended to die out after some time, whereas other strains continued to multiply intracellularly as long as it was possible to keep the individual cultures alive. In this latter instance a true symbiosis existed between the cells of the host and the parasite.

The work of Maximow is of great interest, but it must be pointed out that he used rabbit cells. These cells might contain the factor responsible for sensitization, which may be of a cellular and not humoral nature; hence his observation of the signs of beginning necrosis which reminded him of caseation.

In view of the foregoing observations on the cellular response of the host to the invading parasite, which in general corresponds with the cellular response of the susceptible rabbit, except for the cardinal factor of caseation, the solution of the native resistance of the rat will have to be sought in allergy. The observations of this investigation do not agree with the assertion of Opie (23), who maintained that multiplication of bacilli stimulates the new formation and maturation of epithelioid cells and is probably more important in the production of caseation than is sensitization. In the rat there is continuous new formation and maturation of mononuclears, yet there is no caseation.

Two more observations require consideration. In the first place, it has been repeatedly emphasized that the lesion in the lung of rats is not discrete tubercle formation, but rather a diffuse, granulomatous infiltration of mononuclear cells in which the bacilli survive in large numbers without apparent injury to the cells. As recently pointed out by Lurie (24), tuberculosis, even in the susceptible animal, is characterized by two stages. At first the tubercle bacillus multiplies within the monocytes without injuring them, giving rise to a more or less diffuse accumulation

of mononuclears about the focus by mitosis of preëxisting surrounding cells. At this time the bacilli live more or less in symbiosis with the cells. Later, simultaneously with the development of skin sensitivity to tuberculin, the exudation of fluid into the alveolar spaces, the onset of the first stages of caseation and the formation of discrete, nodular, mature, epithelioid cell tubercles, marked destruction of the bacilli takes place, as demonstrated both by culture and by the paucity of stainable bacilli. This is the phase of intolerance between the tubercle bacillus and the tissues and is characterized by nodular tubercle formation and toxic effects on the host, accompanied by the destruction of the bacilli. Thomas (25) has confirmed these observations in his study of the diphasic nature of tuberculosis. It would appear that tuberculosis in the rat's lung remains largely in the symbiotic or diffuse nontoxic stage, and does not pass on to the later development of a toxaemic, nodular stage, as seen in the susceptible animal. This is to be associated with the long persistence of tubercle bacilli, especially of the bovine type, in the lung, the development of but slight and atypical tuberculin sensitivity, the absence of caseation and the failure of appearance of any evidence of toxaemic symptoms in rats whose lungs are infected by great numbers of bacilli.

Furthermore, in the liver and spleen the bacilli cease growing more rapidly and eventually are greatly reduced in numbers, though they still harbor many tubercle bacilli, especially of the bovine type, even three months after infection. It is noteworthy that in these organs the developing epithelioid cells resemble to a certain extent those seen in the rabbit and human being. In the lung and tracheobronchial lymph node, however, the epithelioid cells have a fundamentally different structure. Instead of the almost homogeneous, extremely finely vacuolated cytoplasm of the former, very large foamy cells occur whose cytoplasm is filled with large uniform vacuoles. These large foamy cells remind one of the first stages of epithelioid cell formation as demonstrated by Sabin and her coworkers (4) with the phosphatide of the tubercle bacillus. As this substance is phagocyted by the monocytes, and as it undergoes finer and finer dispersion in their cytoplasm, the monocytes gradually assume the character of mature epithelioid cells in which the vacuoles of uniform size and extremely minute are collected in the *Hof* of the nucleus, where the rosette of the resting monocytes is found. Since the liberation of the lipoid from the tubercle bacillus and its elaboration by the phagocytes must occur chiefly after the death and disintegration

of the bacilli, it is clear that the more effective the destruction of the bacilli and the more complete the dispersion of its lipoid, the finer and more uniform will be these vacuoles. Immature epithelioid cells are associated with less effective destruction of the bacilli and less thorough dispersing of their lipoids; hence the large foamy epithelioid cells of the lungs of the rat where the bacilli are destroyed on a less extensive scale. In the liver and spleen, however, where the bacilli are more effectively destroyed, the epithelioid cells do not show these large vacuoles, but their cytoplasm resembles more closely that of epithelioid cells seen in the rabbit.

While true caseation does not occur in the rat, the foamy cells gradually disintegrate by coalescence of their vacuoles and disruption of their nuclei. To what extent the lack of development of caseation is due to the failure of the tubercle bacillus to be destroyed in sufficient amounts, and to the incapacity of its tissues to become sensitized to tubercle bacillus protein is problematical.

Tuberculosis in the rat resembles more closely leprosy as it occurs in man or Johne's disease of cattle, where the bacilli remain essentially in symbiotic relation to the cells and where sensitivity to the respective microörganisms is little developed.

SUMMARY

1. Following the intravenous injection of tubercle bacilli the cellular inflammatory changes and fate of the tubercle bacilli were observed by cultural and histological methods over a period of several months.

2. Changes of different degree were caused by the different types of tubercle bacilli. All types stimulated the accumulation and multiplication of mononuclear cells which underwent transformation to young epithelioid cells. Tubercle bacilli multiplied within their substance up to a certain point and then underwent destruction, which varied in degree with the type of bacillus. With the progress of bacillary destruction the epithelioid cells matured and assumed the familiar character of this cell.

3. The cells of the different organs of the body varied in their capacity to destroy tubercle bacilli. Immature epithelioid cells with foamy cytoplasm, characteristic of incomplete destruction of tubercle bacilli, were the rule in the lung, but not in the liver and spleen where destruction of bacilli was more effective.

4. In the lung, following bovine type infection, the bacilli multiplied

rapidly at first, in some cases up to 250 times the original concentration (1,023,000 colonies per 10 mg. tissue at one month as compared with 4,047 at twenty-four hours). After three months the number of bacilli was much reduced. Increase and decrease of bacilli in the tracheobronchial lymph nodes was approximately parallel to that in the lungs.

5. In the liver and spleen large numbers of bacilli localized immediately after infection, and the maturation of the accumulated cells of inflammation developed relatively quickly. Destruction of bacilli was evident as early as the second week, and after that the lesions steadily regressed. However, as late as three months after injection, living bacilli persisted in the cells, apparently in symbiosis, for little evidence of tissue injury was present. Often many more tubercle bacilli could be demonstrated histologically than by culture, a fact suggesting that many bacilli were killed without disintegration. In other cases acid-fast particles, apparently representing destruction of bacilli, were abundant.

6. In the kidneys, lesions were rare and small and the bacilli cultured were few.

7. In early stages of the disease, synchronously with multiplication of bacilli, lesions were diffuse. Later, following the destruction of many bacilli, the lesions became discrete, especially in the liver and spleen. In the lung, where destruction of the bacilli was least effective, the lesions remained diffuse even after three months.

8. Caseation did not develop, but foamy cells tended to disintegrate, following coalescence of their vacuoles and disruption of nuclei.

9. The destruction of many bacilli explains the resistance of the rat to the progress of tuberculous infection, but the persistence of others, in apparent symbiosis with the tissues, without necrosis, caseation or other tissue damage, is correlated with the long and continuing course of tuberculosis in the animal.

In conclusion, I desire to express my indebtedness to Messrs. E. B. Reed and W. Littell, Directors of the Educational Division of the Commonwealth Fund, New York, who made it possible for me to carry out this work. I am also greatly indebted to Dr. G. A. Dick, Dean of the Veterinary School, and Dr. E. R. Long, Director of the Henry Phipps Institute, University of Pennsylvania, Philadelphia, for their permission to undertake and to publish these studies, and for the facilities placed at my disposal in persuance thereof.

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TUBERCULOSIS OF TONSILS AND SKIN[1]

A Contribution to the Theory of the Origin of Langhans' Giant Cells

SIEGFRIED TANNHAUSER

The most conspicuous feature in the case which will be reported is a combination of tuberculosis of the tonsils and the skin. This combination seems to be rare; in our extensive, though not complete, studies of the literature we were not able to find a similar case, although tuberculosis of the tonsils has been reported in increasing numbers in recent publications (1, 2, 3, 4, 5, 6, 7, 8, 9, 10). Three main groups can be differentiated: first, tuberculosis of the tonsils connected with open tuberculosis of the lungs; second, primary tuberculous involvement of the tonsils; third, haematogenous spread into the tonsils. As will be shown later on, our case falls under groups two and three.

At the same time the report on the histological findings is intended to be a contribution to the theory of the origin of the Langhans' giant cells. These cells, present in unusually great numbers, allow in their majority the demonstration of their direct derivation from vascular tissue.

REPORT OF CASE

A. P., a colored woman, thirty-four, with six healthy children, noticed in October, 1939, nightly aching in both shoulders, pain and swelling of the tonsils and increasing weakness. A month later painless lesions on forearms and lower legs appeared. In January, 1940, tonsillectomy was performed which showed tuberculosis of the tonsils. The wound was slow in healing; the patient felt weak for some months after the operation. A chest film showed doubtful swelling of the right hilar lymph nodes and a small cluster of soft shadows in the right second interspace near the lateral chest wall. The back of her hands and the forearms were covered with slightly elevated, painless skin lesions of a dark brownish color. Most of them were sharply demarcated, measuring between 2 mm. and 1.5 cm.; some lesions showed increased swelling with a pinkish color resembling *erythema nodosum*. Similar lesions were seen on the dorsum of each foot. The laboratory findings on

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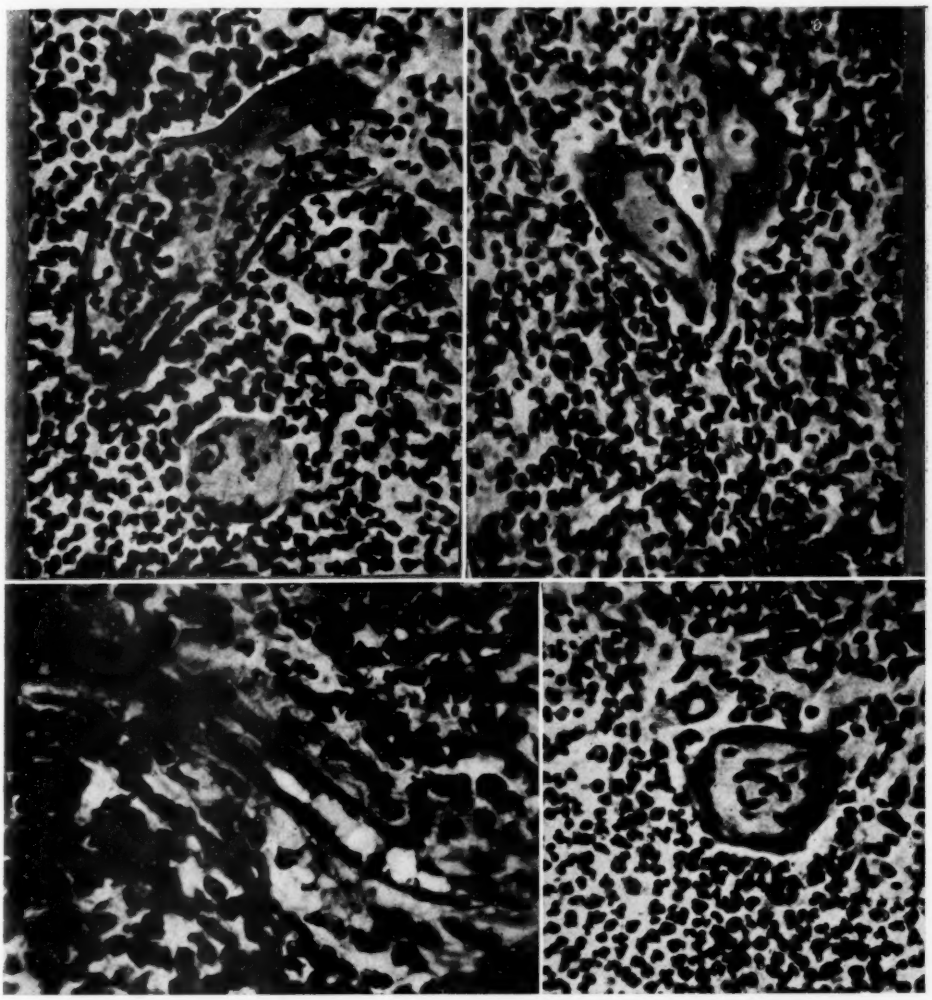
February 14, 1940 were as follows: red cell count 4,200,000; haemoglobin 62 per cent = 8.9 g.; total white count 8,500; neutrophiles 0–0–1–57; 8 monocytes; 32 lymphocytes; sedimentation rate after Westergren was 67 mm. in 60 minutes. A repeated blood count on March 2, 1940 showed no pathological change, but the sedimentation rate was 42 mm. There were no other conspicuous findings. Patient noticed that the skin lesions disappeared and recurred in new locations. After treatment with prolonged hot baths they disappeared entirely. On June 4, 1940, an X-ray film showed complete disappearance of the above mentioned cluster of shadows in the right chest field. One deep lymph node in the neck of the patient was swollen and slightly tender. Patient had gained weight and felt much better.

The gross specimen of the tonsils shows that they are very markedly swollen. On cross-section they show a firm, whitish tissue of a somewhat dryer, more medullar appearance than ordinarily encountered in hyperplastic tonsils. Interspersed in this tonsillar tissue are small yellow spots, distinctly demarcated. On histological examination there is an extensive tuberculosis of both tonsils. In some parts there is formation of single tubercles composed of epithelioid cells, showing heavy infiltration by polymorphonuclear leucocytes and, in some instances, central caseation. These tubercles are mostly located in the sinuses of the lymph nodes; some of them can be seen invading the lymph follicles from the outside. In other parts smaller and larger tubercles are seen within the germinal centres of the lymph follicles. There is an extreme wealth of vascular tissue throughout the whole specimen; in some areas there is dilatation and beginning necrosis of the densely packed capillaries. There are other areas which show no single tubercles but rather an amorphous tuberculous granulation tissue composed of epithelioid cells, giant cells of the endothelial and Langhans type and an extreme amount of blood vessels.

In the Langhans type giant cells in this specimen, one is able to study their origin from vascular buds in all stages of development. One can distinguish capillaries and small arterioles with incipient oedema and coagulation necrosis of their walls. In other vessels this process is further advanced and the whole lumen is filled with a uniform, necrotic mass, staining reddish-blue, within which one can see polymorphonuclear leucocytes and red blood cells. The nuclei are arranged in an annular fashion at the walls of the vessel; one can still see the fibriles of the vascular wall. Other capillaries of similar appearance retain distinct lumina which are filled with red blood cells, lymphocytes and polymorphonuclear leucocytes. One is able to distinguish all transitions from a blood vessel with beginning degenerative changes to a fully

developed Langhans type giant cell. This is particularly evident in observing the arrangement and state of the nuclei of these giant cells. In earlier stages of the development the nuclei are larger, stain rather



FIGS. 1–4

FIG. 1. Upper Left. A capillary bud growing into a tubercle. Partial transformation into a giant cell visible at both poles.

FIG. 2. Upper Right. Capillaries showing direct extension into giant cells.

FIG. 3. Lower Left. Example of degenerative changes in blood vessel (within tubercle). Proliferation of intima, oedema of walls.

FIG. 4. Lower Right. Giant cell with double ring of nuclei. A crosscut of the blood vessel of figure 3 would present a picture like this.

lightly and are arranged in the annular manner of endothelial cells in a crosscut blood vessel. Later stages show massing of the darker pigmented nuclei to one side of the cell until finally many cells show the typical horseshoe arrangement usually encountered in Langhans giant cells.

In some of the pictures presented one can see the direct outgrowth of these giant cells from the capillaries or small arteries. Some of the lymph follicles which do not show tuberculosis are enormously enlarged in size; their germinal centres show a wealth of large polyhedral cells and capillaries.

There are other giant cells of a smaller type within which the nuclei are fewer, more vesicular and do not show the horseshoe arrangement of the typical Langhans giant cell. They appear to derive from the reticuloendothelium of the tonsils; one can see cells with two to six nuclei; in some instances these cells resemble the Sternberg-Reed type giant cells.

A piece of skin removed from a papular lesion of the hand shows tuberculosis of the corium. There are numerous epithelioid tubercles with pallisade arrangement of the cells; however, these epitheloid cells are smaller than usual and more compact; fibroblasts are abundant within the tubercles. There is a sparse infiltration by polymorphonuclear leucocytes and lymphocytes; there are Langhans giant cells, some of them of quite large size. The surrounding corium shows a very slight reaction. No ulceration of the epithelium can be seen.

Discussion of the clinical aspects of the case: The localization of the majority of the tubercles near the crypts in the sinuses of the tonsils and the involvement of regional lymph nodes of the neck make it very probable that the tonsils represent the portal of entry. At the same time systemic, haematogenous involvement is expressed in the haematological findings, the general weakness, the tuberculosis of the skin, some of the tubercles within the tonsils and very probably also in the sparse findings in the lungs. The prompt recession of all these findings after tonsillectomy is remarkable.

Discussion of histological findings: (*1*) The histological findings in the tonsils: tubercles in the vicinity of the crypts and within the lymph sinuses as well as in the germinal centres of the lymph follicles are in favor of a mixed type of infection. There is a possibility that originally the tonsils represented the primary tuberculous focus; from there the tuberculous infection may have spread by way of the lymphatics and the

blood vessels into the hilar lymph nodes, into the skin, lungs and back into the tonsils.

Of some interest is the difference in the histological type of the lesions of the skin and those of the tonsils. Whereas, in general, the productive phase in the tuberculous foci in the tonsils is most conspicuous, there is, nevertheless, a marked admixture of exudative changes as expressed by the abundance of polymorphonuclear leucocytes even in young tubercles. In the skin the changes show a predominantly productive character. There are very few polymorphonuclear leucocytes present; caseation is entirely missing. In some of the tubercles the picture with its marked mixture of epithelioid cells and fibroblasts resembles the picture seen in Boeck's sarcoid. However, the characteristic giant cells, the typical pallisade arrangement of some of the smaller tubercles leave no doubt about the tuberculous nature of the process.

(*2*) Giant Cells: The prevalent opinion on the pathogenesis of tuberculous giant cells encountered in the American literature appears to be that they are some kind of monocytic syncytia. Medlar (11) thinks that the peculiar arrangement of the nuclei of these cells is due to the migration of the nuclei of mononuclear leucocytes to the periphery of dead tissue. Sabin (12) produced multinuclear epithelioid giant cells of the so-called Langhans type by injection of phosphatides from tubercle bacilli into animals. It is her belief that the peculiar arrangement of the nuclei in the periphery of the cell is due to vacuoles which occupy the centre of these cells. According to her opinion the giant cell is formed by continued amitotic division of a monocyte. Other authors believe that the mechanism of the formation of these giant cells is by fusion of many epithelial cells.

That some proportion of tuberculous giant cells, even in many cases the majority of them, are formed in one or the other above mentioned ways, there can be no doubt. A careful study of the epithelioid cells in tuberculous granulation tissue shows many cells with two or more nuclei, cells, which, as in our case, resemble more the Sternberg-Reed type of giant cells than the classical Langhans type.

Whereas the American literature treats the giant cells in tuberculosis as one type, the German literature attempts to distinguish between the different types. Wurm (13), demonstrating the derivation of the Langhans type giant cells from capillary buds, feels that for the Langhans type giant cells an origin from vascular processes seems most likely, although it is possible that this may not be the only method of giant cell

formation. Pagel (14) clearly distinguishes three kinds of giant cells: first, a type which he calls pre-giant cells which are syncytial formations of large mononuclear cells and probably correspond to the cells which Medlar, Sabin and most of the American authors have in mind; second, formations similar to Langhans type giant cells which are degeneration stages of blood vessels, fixed so as to resemble giant cells (15); third, the genuine Langhans type giant cell representing a truly productive formation for which Pagel as well as Wurm could show direct connection with vascular buds. Putschar (16) stresses the occasional wealth of capillaries in tuberculous tissue and comes to similar conclusions as to the connection of these capillaries to the giant cells.

It is obvious that the more blood vessels participate in the formation of the tuberculous granulation tissue the more likely it will become to demonstrate the direct derivation of the Langhans giant cell from these vessels. The case which we have reported, being of that type, furnishes an unusual amount of pictures in evidence of this theory, as the added figures prove.

SUMMARY AND CONCLUSION

A case of tuberculosis, predominantly of tonsils and skin, with minimal lesions in lung and hila, is reported. The histological structure of the tuberculous changes in the tonsils has been presented to some extent in order to demonstrate the vascular derivation of a great proportion of the Langhans type giant cells.

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MEINICKE FLOCCULATION REACTION FOR TUBERCULOSIS[1]

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In the diagnosis of a bacterial infection, the potential value of a serological examination varies inversely with the ease with which the causal organism can be recovered from the patient. Thus, in the laboratory diagnosis of syphilis we rely to a great extent on the circumstantial evidence afforded by the detection in the serum or other body fluid of the specific antibody, because the responsible treponemum is hard to find save in the earlier stages of the disease. In some infections, as for instance in enteric fever, the isolation of the organisms and the demonstration of the specific antibodies are measures equally at the service of the clinical investigator, while in other conditions, for example, certain of the dysenteries, the difficulties in demonstrating the responsible organism are equalled by the uncertainty of serological findings. In the study of tuberculosis, however, the readiness with which the causal organism is to be found in the sputum makes any other diagnostic procedure of secondary importance. Nevertheless, there remain instances of this common infection when the *Mycobacterium tuberculosis* is not easily demonstrable, *e.g.* in miliary tuberculosis, primary effusions into the pleural or joint cavities, intracranial tuberculomata or abdominal or mediastinal lymphadenopathies. In such cases a serological test which would be both specific and sensitive would be a valuable asset in laboratory diagnosis, while a quantitative reaction of assured constancy might prove helpful in the prognosis of pulmonary, orthopaedic or renal tuberculosis in cases undergoing treatment. Many serological reactions have been devised but they have not yielded results sufficiently constant to justify any extensive usage in clinics and sanatoria. The complement-fixation test proved unsatisfactory because of its doubtful specificity; very often false positives occurred in healthy folk who had been infected in early life. For this reason the test has seldom been employed seriously.

The introduction by Meinicke (1934–8) of a flocculation reaction for

[1] From the Osler Pavilion, Radcliffe Infirmary, Oxford.

tuberculosis on the lines of his widely used and eminently satisfactory reaction for syphilis was considered by us of sufficient importance to justify its employment as a diagnostic and prognostic measure in a small series of cases. Unfortunately our enquiry has had to be curtailed because of the difficulty of obtaining the commercial antigen in wartime, but our findings to date are herewith reported.

The sera and fluids were obtained from patients in the Osler Pavilion, Radcliffe Infirmary, Oxford Eye Hospital, Wingfield-Morris Hospital, Berks and Bucks Sanatorium at Peppard Common and the Lord Mayor Treloar's Hospital, Alton: to the medical staffs of these hospitals I express thanks for their kindness in supplying us with the material and necessary clinical particulars.

TECHNIQUE OF THE TEST

Antigens: The original technique (Meinicke 1934) made use of four antigens, a watery, a strong and a weak alcoholic and the ordinary syphilitic antigen (as used in the M.K.R. 11) for control. The test, however, in its present form (Meinicke, Funk and Schultze 1937; Meinicke 1938) requires a strong watery (A), a weak watery (B) and an alcoholic (C) antigen. The first two are kept in cold storage, while the alcoholic may be preserved at room temperature provided the light does not reach it. A special control antigen was at one time recommended in the form of a strong heart extract in an alcoholic medium, but more recently Meinicke (1938) has reverted to employing his ordinary syphilitic antigen (original standard extract for the M.K.R. 11) for this purpose; this recommendation followed his discovering that the addition to the watery bacillary extracts of a small amount of glycerine bouillon in which the bacilli had been grown enhanced the efficacy of the reagent and rendered the strong alcoholic control antigen unnecessary. Syphilitic sera, therefore, may be expected to react strongly to this control antigen; a special but rather laborious technique of absorption has been advocated in such cases if a coincident tuberculous infection is to be sought.

Procedure: (sufficient for ten sera).

All glassware must be clean; 9.5 cc. of 3.5 per cent sodium chloride are added to 0.5 cc. of antigen A in a test tube and a like amount is mixed with 0.5 cc. of B in a second tube. The two test tubes are now placed in a waterbath alongside two other tubes each containing 1 cc. of antigen C. In the same way the control is set up in two test tubes, the one containing 10 cc. of 3.5 per cent sodium chloride and the other 1 cc. of the control antigen D. When a temperature of 56°C. has been reached in all six tubes (and to achieve this temperature it is an advantage to have the waterbath registering a degree or two higher) the three watery solutions are added to the three corresponding

alcoholic liquids and mixed rapidly but thoroughly by pouring from the one tube to the other. After mixing, the three milky antigen suspensions are ripened in the waterbath for exactly two minutes and then removed from the bath and pipetted into the tubes containing the sera as soon as possible and certainly within ten minutes of completion of ripening.

To each specimen to be tested three tubes are allotted into each of which is placed 0.2 cc. of "unactivated" serum and 0.5 cc. of the required antigen suspension. Thus the first tube will contain antigens A and C, the second, B and C and the third, the control antigen D. After being well shaken, they are set aside, being protected from dust and left at room temperature over night. In the morning the results are read, but if the control tube is incompletely negative, or if all tubes are completely negative (and this will be so in most instances) the tubes are again well shaken and then incubated at 37°C. over night. Thus, if the test fails to work at room temperature it has an opportunity of being effective at 37°C.

Reading the results: To read the results the tubes are carefully lifted and held up to a good source of light. In a negative reaction a dark blue and compact sediment is seen occupying the centre of the bottom of the tube. If the tubes are gently inclined at an angle of 45° it will be noticed that the sediment shifts with the tube so as to form blue stripes. The blue color, incidentally, is due to a dye which is an ingredient of the alcoholic antigen.

A *strongly positive* reaction shows as a broad coarse crumbly, grayish-blue deposit with clarification of the supernatant fluid. If the tube is inclined as before the coarse deposit is reluctant to move with the tube.

A *moderate* reaction consists of not quite such a broad deposit and no clarification as in a strong positive.

A *weak positive* amounts to a narrow granulated area surrounding that central blue disc one sees in the negative result; in this type of weak positive reaction the blue disc is unstable and will readily alter its position when the tube is slanted. Sometimes the peripheral zone of granulation is so small as to justify the use of the term *very weak positive*.

RESULTS

The test has been applied to 383 cases of pulmonary tuberculosis and 402 controls of which 44 have been segregated into an observation group because they were admitted to the Hospital on suspicion of being tuberculous, while 26 others have been considered separately owing to a remote possibility of a tuberculous background; they are referred to later. In addition, there were tested the sera of 5 healed cases of pulmonary tuberculosis, 39 instances of nonpulmonary tuberculosis and 27 examples of certain diseases wherein the demonstration of tuberculous antibodies would have been considered of interest.

The results of the control series and of the patients with pulmonary tuberculosis are set out in table 1. The only example in the control group which gave a strongly positive result has been followed up eighteen months after the test and it is certain that a tuberculous infection, either present or past, can be excluded. The subject was a middle-aged woman who was investigated on account of symptoms of diabetes mellitus. It so happened that the chest was X-rayed as a routine part of the investigation and the film proved entirely negative. The sedimentation rate was also negative. Similarly, the 8 cases which gave a moderately

TABLE 1

Meinicke tuberculosis reaction in controls and pulmonary tuberculosis

RESULT	NON-TUBERCULOUS CONTROLS		DOUBTFULLY TUBERCULOUS OBSERVATION CASES		ESTABLISHED CASES OF TUBERCULOSIS									
					TB Minus		TB Plus One		TB Plus Two		TB Plus Three		Pleural effusions	
	Number of sera	Per cent	Number of sera	Per cent	Number of sera	Per cent	Number of sera	Per cent	Number of sera	Per cent	Number of sera	Per cent	Number of fluids	Per cent
Negative	228	68.7	22	50.0	14	23.0	3	10.3	26	23.0	18	10.0	2	4.0
Doubtful (including those with incompletely negative controls)	42	12.7	1	2.3	3	4.9	5	17.2	5	4.4	9	5.0	15	30.0
Very weakly positive (±)	32	9.6	5	11.4	18	29.5	4	13.8	18	15.9	22	12.2	4	8.0
Weakly positive (+)	21	6.3	8	18.2	13	21.3	8	27.6	23	20.6	50	27.8	7	14.0
Moderately positive (++)	8	2.4	4	9.1	8	13.1	6	20.7	22	19.5	36	20.0	10	20.0
Strongly positive (+++)	1	0.4	4	9.1	5	8.2	3	10.3	19	16.8	45	25.0	12	24.0
Total in group ...	332		44		61		29		113		180		50	

positive result have been studied and it seems reasonably certain that tuberculosis can be excluded. It follows, therefore, that of a control series, just under 3 per cent gave a moderately or strongly positive result when a negative was to be expected, while if the weak positive be accepted as definite positives, just over 9 per cent give false positive readings. As a test which gives so high a proportion of false positives is of little value, it becomes necessary to raise the threshold of positivity, at any rate, to the moderately positive level (giving 2.9 per cent of false positives) and ideally to the strong positive level (with only 0.4 per cent of false positives). At the former level the percentage of cases in the

Ministry of Health's classified groups of TBminus, TB+1, TB+2 and TB+3 giving positive readings are 21.3 per cent, 31.0 per cent, 36.3 per cent and 45.0 per cent respectively, or, at the latter level, 8.2 per cent, 10.3 per cent, 16.8 per cent and 25.0 per cent. Thus, although there is a distinct tendency for the likelihood of a positive reaction to increase as the disease becomes worse, the percentage of positives is too low even in the TB+3 group for the test to have any great diagnostic value. Nevertheless, a positive finding would point very strongly to the likelihood of a tuberculous infection, although the small proportion of false positive results in this series would justify caution in attributing an absolute specificity to the test.

It is perhaps a disturbing fact and it is one which greatly limits the value of this test that so definite a percentage as 23.0 of the TB+2 and 10.0 of the TB+3 groups give a completely negative reading. This may possibly be related to the vagaries of smooth and rough variants of the bacillus. One cannot agree, therefore, with Boas and Freudenthal (1936) who state that the test if negative is a comparatively reliable guide in the exclusion of tuberculosis, nor with Kalk and Burgmann (1936) who accept a negative test as evidence of the absence of tuberculosis.

Included under the heading of doubtful results are the borderline, weak positives and those specimens wherein the control remained positive. The high proportions of the latter in the control series is largely accounted for by the number of syphilitic sera employed.

The end column in table 1 is interesting in that it shows that when pleural fluids are used instead of serum and in the same quantity, some 44 per cent of tuberculous effusions may be expected to yield a positive result (only strong and moderate reactions have been accepted). The high proportion of doubtful findings (30 per cent) must be attributed in part to factors in the protein constitution of the fluid which render many of them unsuitable for the particular colloidal conditions which this test demands. Unfortunately, the number of nontuberculous pleural fluids available was too small to be of use as a control series, so that the specificity of the test when applied to pleural fluids has not been assured. A weak positive result was obtained in a pleural effusion complicating lymphadenoma in which no tangible evidence of tuberculosis was forthcoming.

It was noticed that very often a pleural fluid would yield a positive result when the serum was negative; in these instances when both were

positive, more often than not the pleural fluid was more positive than the serum. Thus, it would seem that the test could be of value in cases of primary pleural effusion or tuberculous effusions following lobar pneumonia, if only its specificity could be established.

TABLE 2

Meinicke tuberculosis reaction in miscellaneous cases of tuberculosis

TYPE OF DISEASE	NUMBER OF CASES	RESULT OF TEST				
		Strongly positive	Moderately positive	Weakly positive	Very weakly positive or doubtful	Negative
Abdominal	11	2	2	1	3	3
Calcified lymph nodes (cervical or tracheobronchial)	4	1	—	2	1	—
Epididymitis	2	—	—	—	—	2
Orthopaedic, active	17	1	2	3	5	6
Orthopaedic, quiescent	5	—	—	—	3	2
Pulmonary, healed	5	1	—	3	1	—
Total	44	5 = 11.36%	4 = 9.09%	9 = 20.45%	13 = 29.54%	13 = 29.54%

TABLE 3

Meinicke tuberculosis reaction in certain other diseases

TYPE OF DISEASE	NUMBER OF CASES	RESULT OF TEST				
		Strongly positive	Moderately positive	Weakly positive	Very weakly positive or doubtful	Negative
Erythema nodosum	1	—	—	—	—	1
Iridocyclitis	13	—	1	1	2	9
Leprosy	1	1	—	—	—	—
Lupus erythematosus	1	—	—	1	—	—
Lupus vulgaris	3	—	—	—	1	2
Sarcoidosis	7	—	—	—	2	5

The findings in cases of healed pulmonary and nonpulmonary tuberculosis (regrettably few) are shown in table 2 and of certain other diseases in table 3.

A few joint fluids were tested but in most of them the controls remained positive. The only strongly positive reaction was obtained in a seropurulent streptococcal effusion in which there was no subsequent evidence of tuberculosis. In one specimen of peritoneal fluid, however, in which streptococci were found and the M.TB.R. was strongly posi-

tive, subsequent autopsy revealed an active tuberculous lymphadenitis and a terminal streptococcal peritonitis.

Some 18 cerebrospinal fluids including 4 from cases of tuberculous meningitis were tried; 6 of them failed to give negative controls but the rest were all negative with the exception of one of the tuberculous fluids which gave a weak positive result. It would seem desirable, however, on another occasion to use at least 0.5 cc. of cerebrospinal fluid so as to obtain antibodies in sufficient concentration to react adequately.

In several cases investigated, the Meinicke reaction was repeated on one or more occasions. Although, at first, a few instances were met with in which as the disease developed a serum changed from negative to positive, this proved too unreliable a way of watching the progress of the disease. At first the specialized technique which claimed to be more adapted for prognostic work was used. The essential difference in method consists of slightly increasing the pH of the sodium chloride solution by the addition of 0.01 per cent sodium carbonate and by employing a smaller amount of serum, namely 0.15 cc. This subsidiary test, however, proved more difficult to read and in the cases in which it was used the results were less sensitive than in the main test, so that its employment in prognosis was limited to quite few cases. It was therefore abandoned.

Of the pulmonary cases examined serologically on two or more occasions, 53.6 per cent showed some alteration, usually slight, in the readings. Occasionally this change followed the course of the disease in that the strength of the reaction dropped as the patient recovered, but in an equal proportion of instances the test became more positive as the subject improved. In spite of this fact, which appeared to suggest that the ability to demonstrate antibodies might run parallel with improvement in this disease, no relationship could be found between the length of illness and the strength of the reaction; neither was there any relationship between the age of the patient and the intensity of the reaction discerned. The M.TB.R. and the sedimentation rate (Westergren's technique) were compared on a scatter chart in some 350 cases but no constant relationship was noted. This agrees with the finding of Leitner (1937) but not with that of Hardt (1936) who noted a parallelism. A few authors have studied the reaction in relation to cutaneous tests. Trautwein (1936) and Sartori and Bonezzi (1936) found agreement but Leitner (1938) failed to do so.

COMMENT

A study of the literature reveals a remarkable disparity between the results obtained with this test by different workers. Most of the figures prior to 1937 have been collected by Leitner (1937) and they show that whereas Beuing (1935), for instance, reported 91.3 per cent of cases positive, Jochims' (1935) corresponding figure was only 26 per cent. One author even found many more negative in the established disease than in the control group! Several of these results, however, have been worked out with the earlier technique and some of them either concern too few cases or else are inadequately controlled. A more reliable series was published in 1936 by Bohne. With 1.4 per cent of false positives he obtained his highest figure with disease of moderate severity (97.18 per cent), this being followed by 90.5 per cent in the severe, 61.6 per cent in the slowly progressive, 59.3 per cent in the early and 21.7 per cent in the stationary groups. Leitner's (1937) highest result was in the group with early cavity formation (90 per cent) and his lowest in miliary disease of the lung (53.9 per cent). He speaks of nonspecific positives amounting on the average to 10 per cent, but in one series of controls, 24.8 per cent were positive, mostly weak. In his second but smaller series of cases published in 1938 when the more recent modifications in technique were adopted, he obtained slightly better figures, for out of 116 cases of active pulmonary disease he reported 86.9 per cent as positive; he remarked that, although the sensitivity of the test had increased by reasons of modification in technique, the specificity remained about the same. These results of Leitner are more favorable than those reported here, for if, in our series, the positive line is raised to that of weak positive, only 57.7 per cent of the group of active disease of the lung are positive, while the false positive percentage would be raised to 9.2.

Spies (1938), however, obtained positive results in only 40.5 per cent of cases, a figure more comparable with our own. He adds that negative results are to be expected in cases of acute and fulminating disease and that it is only by finding repeated positive results that the probability of a tuberculous condition can be indicated, a premise which if substantiated would, because of the inconvenience and expense occasioned by repeated performances of the test, detract enormously from any diagnostic value with which it can be credited. With regard to the use of this test in prognosis, he remarks that the reaction runs unmistakably parallel with the progress of the disease only in cases of rapid deterioration, an implica-

tion confirming an impression of the limited usage of this test in predicting the course of this disease. That the test is of little use in prognosis is to be found in the views of Sartori and Bonezzi (1936) and of Leitner (1937, 1938).

Most authors seem agreed that nonpulmonary tuberculosis can be expected to give a lower percentage of positives than open cases of lung disease. Leitner's figures are 66.7 per cent as against 80.3 per cent, while Bohne (1936) gives 31.2 per cent as against 68.6 per cent.

The Meinicke reaction would appear to compare favorably with other recent serological studies. Kolmer and Mahoney (1939), for instance, obtained 63.7 per cent positives in active pulmonary tuberculosis employing the complement fixation test; they advise caution in interpreting this test because 16 per cent of syphilitic sera gave a false positive. Hassegawa and Kochi (1939) using an agglutination test obtained 71 per cent positive in class III cases (Turban-Gerhardt classification), 64 per cent in class II and 43 per cent in class I. Contini (1939), however, in a small series of cases of surgical tuberculosis obtained 82.9 per cent positives with a complement fixation test and only 63.3 per cent with the Meinicke reaction.

It is possible that the Meinicke reaction in skilled hands yields more reliable results than our figures and some other reports would seem to show. Chediak (1938) speaks most highly of it compared with other serological tests which he saw on a study tour in Germany. No doubt, better results might be obtained by submitting the material to the test soon after it is drawn; many of the specimens had to wait a week or more before the examination could be carried out, and an impression was formed that pleural fluids, at any rate, should not be more than four days old; in a few instances portions of the same serum were retested at weekly intervals and little deterioration was noticed if the material had been kept in cold storage, whereas if it had been incubated at 37°C. one could expect the control tube to fail to become negative.

In conclusion, the specificity and sensitivity of this test in its present form leave much to be desired if it is to have a full place in clinical pathology. It could have a limited but definite place in the diagnosis of tuberculosis when bacilli are not readily demonstrable, but its value for a clinician in prognosis seems problematical.

The conflicting reports on the efficacy of this test may be in part explained by the difficulty in deciding what constitutes a positive reaction in view of the spurious results occasionally met with in a control series.

If the good reports of this test (Chediak 1938) are to be substantiated, further studies would be needed with many more cases, and controls and experiments undertaken to ascertain the optimum conditions for its successful performance.

SUMMARY

1. The Meinicke Tuberculosis Reaction has been performed on 427 cases of tuberculosis and 402 controls. An arbitrary standard was reached for the positive level, giving 2.9 per cent false positives.

2. The TB−, TB+1, TB+2 and TB+3 pulmonary cases gave positives of 21.3 per cent, 31.0 per cent, 36.3 per cent and 45.0 per cent and negatives of 23.0 per cent, 10.3 per cent, 23.0 per cent and 10.0 per cent, respectively.

3. Pleural fluids gave 44.0 per cent positive, 4 per cent negative, while some 30 per cent failed to work, because the control tubes remained positive.

4. A small series of nonpulmonary tuberculosis gave 20.5 per cent positive and 29.5 per cent negative.

5. The test in its present state has small value in laboratory diagnosis.

I wish to express thanks to Mr. R. W. Deacon, laboratory technician at the Osler Pavilion, for his industry and valued assistance in the technical part of this study.

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LEUCOCYTES IN TUBERCULOSIS[1]

A Further Test of the Validity of the Pathological Interpretation of Leucocytic Counts in Tuberculous Patients

E. M. MEDLAR

In the American Review of Tuberculosis for June, 1935, the author (1) presented "a test of the validity of the pathological interpretation placed upon the leucocytic reaction" in clinically active pulmonary tuberculosis. The main reason for presenting the data at that time was to place on record an analysis of a group of tuberculous cases that would allow of a follow-up study. It would then be possible to present a revision of the same group and either substantiate or disprove the interpretations already recorded. The author hereby submits a revision of the group of 281 cases that formed the basis of the original report. The status of the cases here presented is concerned with the period beginning in March, 1934 and ending in January, 1940.

For this comparative study the group is reduced to 210 cases. Seventy-one cases have been deleted for the following reasons: (*1*) the 44 deaths recorded in the original report have been omitted since the status of these cases remains the same; (*2*) in 3 instances a follow-up record is not available; (*3*) 24 cases have been reclassified as clinically inactive and for this reason are deleted. Since the original report, all of the tuberculous cases that had been admitted to our institution have been reclassified (by the clinical staff) on a basis of clinical activity. The minimal criterion for clinically active pulmonary tuberculosis used in this reclassification was the demonstrable instability of the lesion as revealed by serial roentgenograms. On this basis, the 24 cases mentioned (*3*) were classed as clinically inactive tuberculosis.

In the reclassification a stricter attitude was taken relative to the classification as to the extent of the disease, so that the present grouping of the cases is not the same as in the previous report. The effect of this reclassification is shown by a reduction from 58 to 32 in the group of far advanced tuberculosis living at the time of the original report. A

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somewhat similar shift has also occurred in the groups of minimal and moderately advanced disease.

In the reclassification of cases noted above, no consideration was given to the leucocytic record of the individuals. The net result, in so far as the leucocytic interpretation is concerned, has been a shift of about 5 per cent toward the favorable pathological group. From this it is apparent that the adoption of the more rigorous clinical standard has not significantly altered the distribution of the cases on the basis of a favorable or unfavorable pathological status.

The pathological interpretation from leucocytic counts remains the same in this study as that used in the previous report. To simplify the study the two unfavorable groups have been combined. The favorable group remains as before.

In our original report, the essential basis for estimating a favorable or unfavorable pathological status was the leucocytic picture of normal healthy persons. Recently our data on leucocytic counts from normal persons has been augmented to over 600 consecutive weekly counts on 50 normal healthy adults. We have 545 leucocytic counts on these individuals at a time when there was no clinical evidence of ill health. A compilation of the leucocytic indices on these counts gives the following distribution: 27 or over, 5 per cent; 26 or less, 95 per cent; 20 or less, 67 per cent. With the greater number of leucocytic counts from a larger group of normal persons the distribution of the leucocytic indices remains practically the same as presented in a previous paper (2). We see no reason, at the present time, for changing the criteria previously adopted for the pathological interpretation of tuberculosis from leucocytic counts. The essence of our theorem is and has been that for a tuberculous case to present a favorable pathological picture, a normal leucocytic picture must be maintained when consecutive leucocytic counts are taken.

In the tabulations which are presented in this paper the status as to "work," "incapacitation" and "death" is presented. The heading "work" designates that the person is able to work and that there has been no clinical evidence of any activity of the tuberculous infection. The heading "incapacitation" indicates that at some time during the period of observation (March, 1934 to January, 1940) definite evidence of recrudescence of the tuberculosis, requiring medical care, has occurred. Persons in this category may be at work at the time of this report or they may still be under the care of a physician; they all have shown an

unstable course in their disease. The heading "death" indicates death from tuberculosis, unless otherwise specified. It is to be remembered that all the individuals in the group had been discharged from the hospital and were alive at the time of the original report in 1935. The tabulations used in the present article correspond to similar tabulations in the previous report.

Table 1 presents the status in 1934 and in 1939 of the 210 cases divided into favorable and unfavorable pathological groups.

In table 1 the group as a whole shows fewer at work, fewer incapacitated and several deaths in 1939 as compared with 1934. It is interesting to note that nontuberculous deaths have occurred in both groups and that of the 14 tuberculous deaths, 13 have occurred in the unfavorable pathological group. One in 66 in the favorable and one in 11 in the

TABLE 1

Status as per original report and as from 1934–1939 of a group of 210 tuberculous cases

PATHOLOGICAL GROUP	STATUS AS OF 1934				STATUS AS OF 1939			
	Total	Work	Incapacitation	Death	Total	Work	Incapacitation	Death
Total	210	141	69	0	210	134	57	19*
Favorable	66	58	8	0	66	57	5	4*
Unfavorable	144	83	61	0	144	77	52	15*

* 5 nontuberculous deaths—3 in the favorable and 2 in the unfavorable pathological groups.

unfavorable group died from tuberculosis during the period from March, 1934 to January, 1940.

It is impossible to illustrate in table 1 the shifts that have occurred in individual cases within the groups. To illustrate this phase table 2 is presented. A change in status has occurred in 49 of the 210 individuals. In 44 instances this change has been due to the tuberculous infection, and in 5 instances the change has been due to a nontuberculous death.

Table 2 shows that the unfavorable pathological group was the more unstable in that there was a change of status in 36 cases (25.3 per cent), whereas in the favorable group there was a change of status in 8 of the cases (12.7 per cent). The difference between the favorable and unfavorable is also emphasized by the fact that 13 out of the 15 relapses and 13 out of the 14 tuberculous deaths occurred in the unfavorable group. The difference between the ability of the individuals in the two groups to return to work and remain for a five-year period without

further relapse is shown by the fact that 5 out of 8 in the favorable group attained this record, while only 10 out of 59 in the unfavorable group presented a similar record. It is quite evident that the percentage of change for the worse is greater in the unfavorable than in the favorable pathological group. This trend, as evidenced by a revision of the group

TABLE 2

Status in 1939 of cases at work or incapacitated in 1934; nontuberculous deaths have been omitted in the group

PATHOLOGICAL GROUP	TOTAL	STATUS IN 1939 OF CASES AT WORK IN 1934				STATUS IN 1939 OF CASES INCAPACITATED IN 1934			
		Total	Work	Incapacitation	Death	Total	Work	Incapacitation	Death
Total	205	138	119	15	4	67	15	42	10
Favorable	63	55	52	2	1	8	5	3	0
Unfavorable	142	83	67	13	3	59	10	39	10

TABLE 3

Status in 1939 of cases at work or incapacitated in 1934 on the basis of the pathological groups and the extent of the disease

EXTENT OF DISEASE	TOTAL	STATUS IN 1939 OF CASES WORKING IN 1934				STATUS IN 1939 OF CASES INCAPACITATED IN 1934			
		Total	Work	Incapacitation	Death	Total	Work	Incapacitation	Death
Favorable Pathological Group									
Total	63	55	52	2	1	8	5	3	0
Minimal	30	28	27	1	0	2	2	0	0
Moderately advanced	26	24	23	1	0	2	1	1	0
Far advanced	7	3	2	0	1	4	2	2	0
Unfavorable Pathological Group									
Total	142	83	67	13	3	59	10	39	10
Minimal	35	22	19	3	0	13	6	7	0
Moderately advanced	82	48	40	7	1	34	3	26	5
Far advanced	25	13	8	3	2	12	1	6	5

reported on in 1935, materially supports the significance of leucocytic counts in tuberculous cases.

In the original report data were given as to the status of the cases when segregated into minimal, moderately and far advanced groups. To complete the data on the present revision, table 3 is presented.

In table 3 the size of the groups is too small to warrant an exhaustive

analysis. When we compare the favorable and unfavorable groups in the different stages of the disease relative to ability to stay at work or to return to work without further trouble from their disease, one finds a distinctly more favorable trend in the favorable than in the unfavorable group. Further conclusions are hardly warranted as there are several divisions that contain too few cases to permit a satisfactory comparison.

SUMMARY

A revision of a group of tuberculous patients reported on five years previously is presented. During this period there has occurred a change of status in 44 out of 205 cases. In the favorable pathological group, a change in status has occurred in 8 cases (12.7 per cent), for the better in 5 cases (7.9 per cent), for the worse in 3 cases (4.8 per cent). In the unfavorable group, the status of 36 cases (25.3 per cent) has changed, for the better in 10 cases (7 per cent) and for the worse in 26 cases (18.3 per cent). Relapse has been about three times more frequent and death from tuberculosis has been over five times more frequent in the unfavorable pathological group. Nontuberculous deaths, however, have been more frequent in the favorable (4.5 per cent) than in the unfavorable (1.4 per cent) group. These data give substantial support to the pathological interpretation, through the circulating leucocytes, presented in the original report in 1935.

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THE LAW OF SMALL NUMBERS

As Applied to Virulence Measurement

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THE PROBLEM

A standard, objective method for measurement of virulence of *Mycobacterium tuberculosis* does not seem to be recorded in the literature. The answer to the problem of the possible transformation of bovine to human type of bacillus *in vivo* or *in vitro* may come from virulence measurement rather than determination of cultural characteristics. In his comprehensive work on dissociation of *M. tuberculosis*, Frimodt-Möller states (1, p. 114):

> In no case did the experiments . . . result . . . in a transformation of bovine to human strains. Were the question asked whether in nature there is not a spontaneous dissociation or transformation of dysgonic bovine strains to eugonic, possibly entirely human types, the answer would be that the relative facility with which bovine strains *in vitro* were observed to assume all the attributes of the human type from the point of view of growth, in conjunction with a general attenuation of virulence, makes such a possibility more probable than was thought earlier.

The value of present methods for measuring virulence may be judged from results such as the following, in two recent publications. Lange (2) injected 86 guinea pigs with doses of tubercle bacilli ranging from one-ten millionth to one-billionth milligram. Seven of these became tuberculous from doses containing 0.2 of one bacillus, 3 from 0.1 of one bacillus and one guinea pig from 0.01 of one bacillus. Lange noticed the incongruity between his culture and guinea pig data but attributed it to imperfect laboratory technique. Undoubtedly, his perplexity over the results would not have arisen had *Poisson's Law of Small Numbers* been brought to the attention of research workers sooner. It happened nineteen years before the publication of Lange's paper, when "Student" (3) published a paper *On the Error of Counting with a Haemocytometer*, in which he showed how the above law explained the manner

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in which yeast cells distributed themselves over the squares in a haemocytometer.

Jensen and Frimodt-Möller (4) reported that out of 15 strains 7 infected guinea pigs in doses containing less than one bacillus. The fractions range from 0.042 to 0.88 bacillus. For their other 8 strains, the minimum infecting doses range from 1.1 to 7 bacilli. Results such as the foregoing become understandable when the distribution of small numbers of bacteria in a fluid medium is viewed statistically.

DISTRIBUTION OF SMALL NUMBERS OF BACTERIA IN A FLUID MEDIUM

> The underlying assumption by which estimates are made of a bacterial population density, from the results of the successive dilution technique . . . is that the individual bacteria are *randomly* distributed in their medium; so that if, for example a sample of 1 cc. is taken from 100 cc. of solution, each bacterium in the whole solution enjoys an *independent* chance of 1 out of 100 (probability = 0.01) of being caught up in this sample. (5)

Random distribution of small numbers of tubercle bacilli or other particles in a fluid medium, results in their non-uniform distribution, even in the complete absence of tendency to agglutination. This is easily seen when a suspension of red blood cells flows freely over the squares of a haemocytometer or when a suspension of single tubercle bacilli flows freely over the squares of a Petroff-Hausser counting chamber.

The *Law of Small Numbers*, as Poisson's series of probabilities is sometimes called, is treated extensively in the literature. Numerous applications to problems in microbiology may be found in the works of "Student" (3), Fisher (6) and Snedecor (7). In this paper an attempt is made to show what this law is and the bearing it has on virulence measurement with doses containing small numbers of live bacilli.

APPLICATIONS OF POISSON'S LAW OF SMALL NUMBERS

Example 1: Use of probability table 1. This is an adaptation of a larger, labor-saving table by Soper (8). An investigator counted a suspension of single tubercle bacilli and found, for example, 3,000,000 per cc. This was diluted so that one litre of final dilution contained 3,000 bacilli, or a mean number of 3 bacilli per cc. The former figure, 3,000,000 per cc., is an actual count which can be made with little error. The latter figure, 3 bacilli per cc., is merely a calculation. Assuming that there is no agglutination or other factor interfering with random distribution and that all 1,000 cc. in the above litre are well mixed, both

theory and practice agree that every single cubic centimetre will *not* contain 3 bacilli.

The theoretical distribution of bacilli throughout the litre is shown in table 1, sixth column, headed "3." This states that 0.05 (top of sixth column) of the above litre, or 50 separate, scattered cubic centimetres, each contain zero bacilli (top of first column). The next line states that 0.15 of the above litre, or 150 separate cubic centimetres, each

TABLE 1

Adaptation of the Law of Small Numbers to show the numbers of tubercle bacilli in assumed equal doses

NUMBER OF BACILLI IN ONE UNIT VOLUME OR IN ONE DOSE	MEAN NUMBER OF BACILLI IN ONE UNIT VOLUME OR IN ONE DOSE, CALCULATED FROM ACTUAL COUNT AND DILUTIONS							
	0.1	0.5	1	2	3	4	5	10
	Probabilities							
0	.90	.61	.37	.14	.05	.02	.01	
1	.09	.30	.37	.27	.15	.07	.03	
2	.005	.08	.18	.27	.22	.15	.08	
3		.01	.06	.18	.22	.20	.14	.01
4			.02	.09	.17	.20	.18	.02
5				.04	.10	.16	.18	.04
6				.01	.05	.10	.15	.06
7					.02	.06	.10	.09
8					.01	.03	.07	.11
9					.003	.01	.04	.13
10							.02	.13
11							.01	.11
12								.09
13								.07
14								.05
15								.03
16								.02
17								.01
18								.01

contain one bacillus. The last figure in the sixth column, 0.003, indicates that three-thousandths of the above litre, or 3 separate cubic centimetres, each contain 9 bacilli.

A 10 cc. syringe full of this well mixed suspension will deliver 1 cc. doses, each of which may contain anywhere from zero to 9 bacilli, the mean, or average number, being 3. Assume that each of 100 such filled syringes are made to deliver a single dose of 1 cc. Among these 100 doses, 5 will contain zero bacilli, 15 will contain 1 bacillus each, 1 dose will contain 8 bacilli, as indicated in the column headed "3."

Example 2: Determination of the number of viable bacilli in a dose. To determine the number of viable tubercle bacilli in doses of one-millionth milligram injected into guinea pigs, Frimodt-Möller (1, p. 211) seeded each of 10 tubes of Loewenstein's medium with this dose of the same suspension. After incubation these tubes showed the following numbers of colonies: 1, 2, 2, 9, 9, 7, 2, 1, 0, 0. If each inoculum really contained one-millionth mg. of single tubercle bacilli, how can the variation in colony count be explained? A total of 365 similar Loewenstein tubes were seeded with this dose of a number of human and bovine strains grown in Besredka fluid medium. Variation in colony count always occurred.

A reasonable interpretation of the above count is: According to this investigator's calculations, every dose of 0.1 cc. that was seeded, contained one-millionth mg. of single tubercle bacilli, as if these were distributed uniformly throughout the suspension fluid—saline solution—in this case. In fact, the distribution is shown by the above counts of 3.3 mean number of colonies per tube.

Do these counts follow the *Law of Small Numbers?* Not exactly. In table 1, the column headed "3" indicates that there are 5 chances out of 100 (probability = 0.05, top of column) that any one of the above set of 10 tubes would contain zero bacilli. The theoretical expectation is, therefore, 0.05 × 10 tubes, or 0.5 tube to be sterile. Actually there were 2 sterile tubes, or 4 times the theoretical. There are 3 chances out of 1,000 (probability = 0.003, bottom of column headed "3") that any one of the above set of 10 tubes will contain 9 colonies. The theoretical expectation is 0.003 × 10 tubes, or 0.03 of one tube. Actually there were 2 tubes, or 67 times the theoretically expected number.

It is not to be expected that one set of 10 tubes will yield exactly theoretical colony counts. But, as the number of tubes is increased, the colony count distribution will approach more and more closely to the theoretical probabilities shown in table 1, provided: (*a*) that the random distribution of small numbers of live bacilli is not interfered with by large numbers of dead bacilli, and (*b*) 10 or more tubes are used in one determination of the number of viable bacilli in the dose injected. The mean number of colonies per tube is seldom reliable when calculated from a set of 3 or 4 tubes, as practiced only too frequently. According to Corper and Cohn (10): "In our hands exact enumeration of colonies has never proved feasible . . ." This may be due to the absence of a statistical approach to the problem.

Frimodt-Möller (1) seeded 72 tubes, each with one ten-millionth mg. of presumably single bacilli, originating from 9 strains. Resultant colony counts were: 43 tubes with zero colonies, 23 tubes with one colony in each, 4 tubes with 2 colonies and 2 tubes with 3 colonies in each, as shown in table 2. The mean number is 37/72, or 0.514 colonies per tube. This actual distribution is almost exactly the theoretical, as indicated by the column headed "0.5" in table 1.

Theoretically, there should be (top of column) 0.61×72 or 43.9 sterile tubes; actually there were 43. The agreement is remarkable since the foregoing statistical considerations apparently did not form a part of Frimodt-Möller's long series of studies on dissociation of *M. tuberculosis*. With doses 10 and 100 times those mentioned in table 2, the colony counts were not distributed in conformity with the *Law of Small Numbers*. A reasonable guess is that a comparatively large number of dead bacilli interfered with random distribution of viable bacilli.

TABLE 2

Comparison between actual colony count distribution and theoretically expected numbers: 72 tubes seeded with one ten-millionth mg. tubercle bacilli by Frimodt-Möller

NUMBER OF COLONIES IN ONE TUBE	NUMBER OF CULTURE TUBES	
	Actual	Poisson theoretical
0	43	43.9
1	23	21.6
2	4	5.8
3	2	0.7

If the above 72 doses had been injected into guinea pigs, 43 or 44 would have received zero bacilli.

Example 3: Reason for infection with smaller dose, when larger dose did not infect.

Strain T1521 (virulent, human type) produced tuberculosis in a guinea pig inoculated with one hundred-millionth mg. while the one inoculated with one ten-millionth mg. or ten times the first dose did not show any sign of tuberculosis. . . . We find that this experience supports the conception that the discrepancies are due only to the different resistance of the individual guinea pigs. (Jensen and Frimodt-Möller (4))

How many live bacilli were in these doses? The available data are: 4 Loewenstein tubes (1, p. 173) were seeded with doses of one ten-millionth mg. of strain T 1521, at time of guinea pig injection. Colony

counts were 1, 1, 1, 0. A larger number of tubes, preferably 20, would give a more reliable mean. The mean number, $\frac{3}{4}$ colonies (or bacilli) per tube, is near enough to one to use the column headed "1" in table 1. There are 37 chances out of 100 (probability = 0.37, top of column) that any one of the above doses of one ten-millionth mg. will contain zero bacilli. Or, out of 100 such doses, 37 will be sterile. Purely by chance, the above mentioned guinea pig, scheduled to receive one ten-millionth mg. tubercle bacilli, received such a sterile dose. Another possibility is that this guinea pig received 1, 2, 3 or 4 bacilli in the dose, but was so resistant that no sign of tuberculosis appeared.

The first of the above mentioned 2 guinea pigs (no. 1065) was exceptional in so far as the dose of one hundred-millionth mg. of tubercle bacilli produced tuberculosis in only 2 out of 27 guinea pigs (1, pp. 65, 83). How many live tubercle bacilli infected guinea pig 1065? According to the investigators, it was 0.098 of one bacillus. Using the only available data—the above mean of $\frac{3}{4}$ colonies per tube seeded with one ten-millionth mg.—doses of one hundred-millionth mg. contained a mean of one-tenth of $\frac{3}{4}$ bacilli, or very nearly 0.1 live bacillus per dose, or one bacillus in 10 doses. According to table 1, column headed "0.1," 90 doses out of 100 will be sterile, 9 out of 100 will each contain one bacillus and 5 doses out of 1,000 will each contain 2 bacilli. Random distribution brings this about. By chance, guinea pig 1065 received 1 or 2 bacilli in the dose. "Extreme tuberculosis" followed.

The number of virulent bacilli per milligram of vigorously growing culture varies according to different investigators. In guinea pigs infected with doses of one hundred-millionth mg., Corper's strains (9) produced tuberculosis in 66 out of 66, Lange's (2) in 9 out of 41 and Frimodt-Möller's (1) strains in 2 out of 27.

SUMMARY

1. A syringe full of a suspension calculated to contain one tubercle bacillus per dose will deliver doses containing zero bacilli 37 times out of 100 trials.

2. A syringe full of a suspension calculated to contain 5 tubercle bacilli per dose will deliver doses containing zero bacilli one time out of 100 trials.

3. When a suspension is calculated to contain 10 bacilli in each dose, the doses delivered will contain anywhere from 3 to 18 bacilli, distributed in accordance with *Poisson's Law of Small Numbers.*

4. Theoretically, it is not possible to inject guinea pigs or seed culture tubes with equal, small numbers of bacilli.

5. The conclusion that a bovine strain has been transformed into a human strain because virulence was diminished may be faulty because no attention has been given to the possibility of sterile doses when small numbers of live bacilli per dose were used. These sterile doses come to light when, with "equal doses," some guinea pigs develop no tuberculosis; some culture tubes remain sterile when determining the number of live bacilli in doses used.

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THE DERMATO-PULMONARY REACTION[1,2]

I. Behavior of the Dermato-Pulmonary Reaction in Artificial Pneumothorax

S. PUDER

INTRODUCTION

Pain occurring with pleurisy, especially of tuberculous origin, is often treated with blisters applied on the skin overlying the diseased organ. The question arises whether this procedure causes only an alleviation or whether the action has a real basis. An attempt was made to answer this problem by an experimental approach, and we have found in preliminary experiments with rabbits (Orvosi Hetilap, 1938, Nr. 17) that (*1*) rabbits treated with mustard plaster showed no significant changes; (*2*) on the skin of the rabbits treated with an ointment containing iodine and potassium iodide, ulceration and demarcation of the ulcers and an oedematous imbibition of the parietal pleura could be observed; (*3*) when treated with tincture of iodine, the skin, the underlying layers and the pleura became oedematous, and there was a congestion in the lungs and a hyperaemia below the pleura; (*4*) the gross changes found in rabbits after a treatment with a mixture of irritants (Rheumapax) were, except for abrasion of the skin, identical with those in rabbits treated with tincture of iodine. The microscopical examination showed severe changes of the skin and subpleural hyperaemia and an escape of serum in the deeper parts of the lungs. So we may conclude that certain substances are, on application upon the skin of the chest, apt to produce hyperaemia, serous effusion or congestion in the visceral pleura and the lung of the same side. This pathological process is called by us dermato-pulmonary reaction.

The question as to the pathogenesis of the changes produced by this reaction must be answered, for a simple deep action of the irritant applied upon the skin can be imagined. The inflammation might spread di-

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[2] Based on lectures read before the Hungarian Society on Dermatology, November 11, 1937, the Association of Hungarian Tuberculosis Dispensary and Sanitarium Physicians, December 14, 1939 and the Budapest Royal Medical Association, February 23, 1940.

rectly from the skin through the subcutis, the musculature and parietal pleura to the visceral pleura. Assuming the tissue reaction ensues in this direct manner it could be prevented by an artificial division of the two pleural layers, that is, by an artificial pneumothorax. Consequently, experiments were made, producing, and maintaining for a certain time, an artificial pneumothorax, while irritating the skin of the thorax on the same side at regular intervals. At the end of the experiments an examination of both lungs was made.

Bergmann, Friedrich and Bokor, Januschke, Delezani, Molitor and Ruhmann have studied the curative action of the skin stimulation upon the adjacent organs. Ruhmann administered heat to the skin of the upper abdomen and observed visible peristalsis by X-ray examination. Similar peristalsis and pyloric reaction could be produced by brushing the skin. The response of the stomach was always preceded by changes in the skin vessels. Ruhmann stated that the hyperaemia represented the primary response of the skin irritation and he made an attempt to verify this view by irritating the skin with chemicals. Application of cold to the skin of the abdomen inhibits peristalsis. Ruhmann could influence the stomach secretion by means of mustard meal placed on the skin. Of 13 experimental subjects, 9 responded with increase of hydrochloric acid and total acid contents. In 2 further cases of anacidity, the appearance of free hydrochloric acid and the increase of the total acids could be obtained by Marinello's procedure. The failure of the effect after blocking the nerve paths by anaesthesia is in favor of the reflex character of this reaction. The best known correlation is that between kidney and skin. Delezani and Wertheimer reported on animal experiments in which the urinary output was increased on refrigeration; the phenomenon was explained by dilatation of the renal vessels. The increase of the urinary output caused by cold or hot baths is a common fact. Eppinger and his coworkers were led by the same experience in their attempt to fight against anuria by the application of diathermy. With reference to this fact, Brings and Molitor applied diathermy to Head's reflex-zone of the kidney. They found an enhanced diuresis after diathermy and refrigeration. The authors concluded that the response had been elicited by irritation of the sensory nerves of the skin. The reflex nature of this phenomenon can still more clearly be shown on nephrectomized dogs, the result of refrigeration being absent on the operated side. In further experiments they observed the augmentation of the urine by cantharides, mustard oil or capsicum, when adminis-

tered to the skin according to Head's zone of the kidney. In this connection, Zack's reflex sign should be mentioned, namely, redness of the skin in diseases of certain organs produced by a vascular reaction. Thus a crescent-shaped redness is often visible over the manubrium in diseases of the aorta. In other patients suffering from similar diseases a circumscribed redness of the skin can be elicited by mechanical irritation. Erythema on the same basis has been described in pulmonary diseases, apart from other authors, by Soós. The phenomena outlined may be called viscero-motoric reflexes.

EXPERIMENTAL

The rabbits were divided into four groups. In the first group, skin irritation only, in the second group (controls) pneumothorax only was applied. In the third and fourth groups pneumothorax was maintained while skin irritation was applied.

Experiment 1: The back of the rabbit was depilated on both sides and the skin of the right side of the thorax was rubbed with a mixture containing lactic acid, orthophosphoric acid and etheric oils in a basic substance made up of alcohol and glycerine, over an area measuring about 5 by 5 cm. (the above preparation is marketed as Rheumapax). The treatment lasted for twenty-nine days. The rabbits were killed by a blow upon the occiput. On autopsy the treated skin area was found bereft of its epithelium. The right lung was moderately distended, pinkish, its surface covered with haemorrhagic areas the size of a pinhead or somewhat larger. The left lung was intact. Microscopical examination revealed marked hyperaemia in the lung of the treated side, in some areas infiltration of the interalveolar septa with eosinophil leucocytes and circumscribed serous collections in some air-cells. In other places, atelectases of small extent, hyperaemia and serous exudation were marked, particularly in the subpleural regions. In the lung of the left, the control side, some atelectatic areas could be seen without hyperaemia or haemorrhages.

Experiment 2: Only right pneumothorax was applied. The treatment lasted four weeks; four insufflations were made with from 80 to 100 cc. of air at each treatment. On autopsy a collapsed fleshy lung was found with atelectasis, especially of the upper lobe. No serum was found in the right thorax. The left lung showed no alteration. Micro-

scopically, collapsed air-cells without any cellular reaction, without marked hyperaemia or haemorrhages were seen. In the left lung only a moderate atelectasis and partly dilated air-cells could be seen.

Experiment 3: Pneumothorax and skin irritation, both on the right side, were performed. The pneumothorax was maintained for twenty-eight days during which time four insufflations were made at equal intervals, each with from 80 to 100 cc. of air. At the beginning and the end of each insufflation, roentgenograms were taken (figure 1). On the seventh day after the insufflation, the right side of the chest was depilated and an area, similar to the one in experiment 1, was treated with Rheumapax for twenty-one days, that is. to the end of the experiment. On autopsy the right upper and middle lobes were atelectatic, bluish-red; the lower lobe was distended, pinkish; the left lung was pinkish and markedly distended. Microscopical examination showed that the air-cells of the collapsed right lung were greatly narrowed or, at some places, had completely vanished (figure 2). The lung tissue was cellular, hyperaemic; the narrow alveoli were filled with detached epithelial cells, red blood corpuscles and, to a lesser extent, with lymphoid cells. In some parts the epithelial cells of the collapsed alveoli were swollen, the bronchi were dilated and in the larger ones a secretion abounding with leucocytes could be seen. The left lung showed normal air content in contradistinction to the opposite lung (figure 3); wide air-cells with a low respiratory epithelium were present and a thin peribronchial halo could occasionally be seen. In the perihilar parts, atelectasis of slight degree with a minimum serous effusion could be demonstrated.

Experiment 4: This experiment was identical with the former. The films made at the beginning and the end of the insufflation series are shown in figure 4. On autopsy, the skin of the right chest was partly covered with crusts. The right pleural cavity was free, no fluid was present; the surface of the collapsed lung was mottled with reddish-brown spots, the size of a millet-seed to a pea. The left lung was distended and pinkish. Microscopically, the epithelium of the skin of the right chest was at some places detached and replaced by loose bloody crust, abundantly interwoven by leucocytes. The cutis showed oedematous imbibition; it was spongy and its superficial layers were at some places densely filled with leucocytes. There was a moderate hyperaemia in the right lung with collapse of some groups of air-cells.

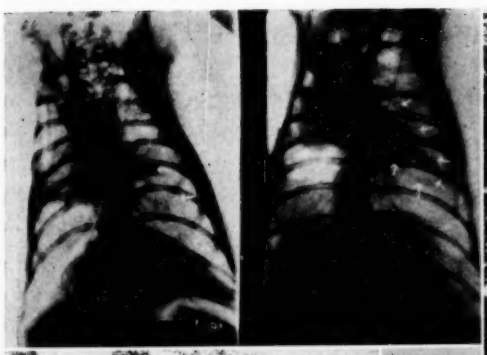

FIG. 1

FIG. 2

FIG. 3

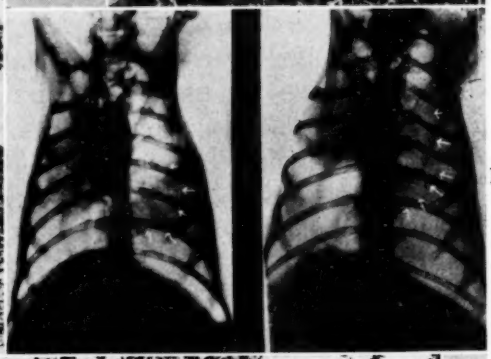

FIG. 4

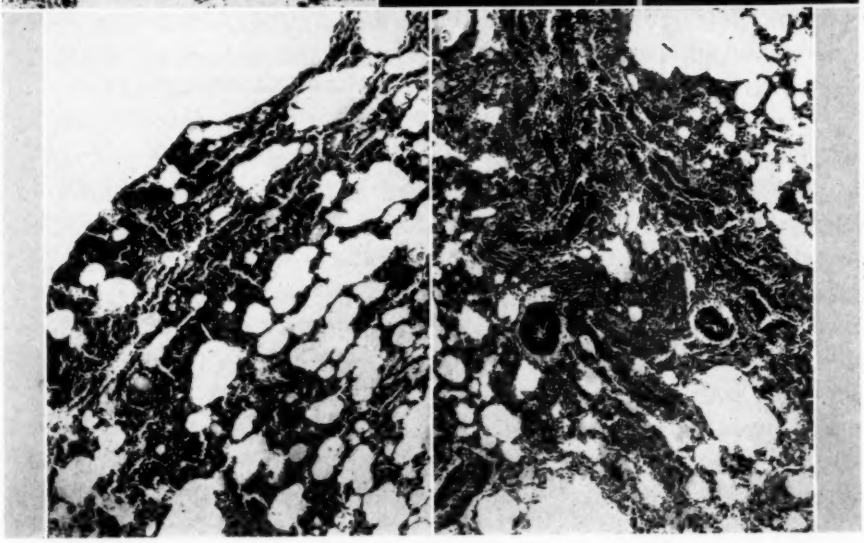

FIG. 5

FIG. 6

FIGS. 1–6

The hyperaemia was most pronounced in the subpleural parts (figure 5). The dilated vessels were surrounded with a thin layer of leucocytes. In the collapsed lung small haemorrhages were present as well as some groups of alveoli, distended with sanguineous serum. In the left lung only a slight hyperaemia could be seen (figure 6); no haemorrhage was present. In the peribronchial areas were small spots of atelectasis, and, contrasting with it, at other places were groups of dilated alveoli.

In summarizing these results, stress should be laid on the following facts: the skin irritation was applied in experiment 1 for twenty-nine days. In the lung of the same side the signs of a marked inflammatory response could be demonstrated. In the experiments published in a previous paper, an irritation lasting only twelve hours had been applied; the resulting response, according to the shorter duration of blistering, consisted only of subpleural hyperaemia, moderate diapedesis of red corpuscles and a slight escape of serum into alveoli. It may be thus concluded that by longer irritation an inflammatory reaction can be produced in the lung of the irritated side.

Pneumothorax was established in experiment 2 in order to learn whether or not a difference existed between the lungs when treated only with pneumothorax or pneumothorax and blistering. It may be stated that the difference is essential, for in the lung of the rabbit treated with insufflation only no cellular reaction, pronounced hyperaemia or haemorrhages were associated with atelectasis, whereas in experiment 3 the rabbits treated with insufflation and skin irritation presented beside atelectasis all the histological features of an intense inflammatory reaction.

SUMMARY AND CONCLUSION

1. Blistering of the skin of long duration produces an inflammatory response in the lung of the same side.

2. Air insufflation alone elicits no inflammatory response in the lung.

3. Skin irritation associated with pneumothorax treatment produces an inflammatory reaction in the homolateral lung.

It may, therefore, be concluded that the dermato-pulmonary reaction is not produced by a continuous spread, but, to all appearances, by an action elicited by a reflex mechanism. The production of the dermato-pulmonary reaction by intervention of the nervous system has been rendered probable by these experiments. The demonstration of this

assumption in a direct manner should take place by the direct examination of the nervous elements taking part in the reaction. This is the subject of the next paper.

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THE DERMATO-PULMONARY REACTION[1]

II. Changes in the Nervous System Associated with the Dermato-Pulmonary Reaction

S. PUDER

In a previous paper (I) experiments were reported which showed that pneumothorax by itself does not give rise to inflammatory reactions in the lungs and blistering of the skin combined with pneumothorax causes an inflammatory response. Thus the dermato-pulmonary reaction arises not by continuous spread but by a reflex mechanism. This statement can be proved indirectly by examination of the nervous elements taking part in the reaction.

Before reporting our own experiments, let us examine the reflex mechanism associated with the diseases of the lungs and the internal organs in general and the data elicited by experimental research.

In the beginning of this century the "light touch palpation" was advocated by Pottenger for the palpation of tuberculous cavities. He started from the fact that over tuberculous lungs a pit is formed by a local atrophy of the skin, subcutis and muscles overlying the cavities and that this atrophy can be recognized by delicate palpation. This symptom can frequently be observed and it has been explained as due to a reflex from the lung, manifesting itself in the skin and the muscles by way of the autonomic nervous system.

A similar organ reflex has been observed by Baráth. He found mydriasis elicited by adrenalin in 12 out of 18 cases of pleural adhesions and in acute abdominal diseases. In the opinion of Sergent, Perin and Alibert, inequality of the pupils produced by poisons of the autonomic nervous system is a significant initial sign of pulmonary tuberuulosis. Otherwise the occurrence of inequal pupils has been observed for a long time in scar formation in the apices, enlargement of the peribronchial lymph nodes and in aneurysm of the aorta, either as a viscero-pupillary reflex or as a direct mechanical effect (Williamson, Roque, Ogle, Seeligmüller, Destrée, etc.). The difference in the size of the pupils is, ac-

[1] From the Dispensary and Department of Pulmonary Tuberculosis of the National Social Insurance Institute of Hungary at Pestszenterzsebet, near Budapest.

cording to Baráth's observations, caused by the increased irritability of the sympathetic nervous system.

Head found independently of, yet in accordance with, Mackenzie that in diseases of certain organs the skin area corresponding to the organ becomes "tender." Skin irritations producing no pain at other places cause a pain in these areas. The segment innervation of the painful area and that of the diseased organ is identical. Unilateral "goose-skin" is likewise a segment reflex. The tuberculin reaction is stronger on the side of the affected lung than on the otherside. The difference is due, apart from the vasomotor innervation, to the alteration of the tissue chemistry in the area of the respective segment.

Also in pneumonia the presence of a homolateral mydriasis can be observed. Further characteristic features are the disproportion of body attitude, the increased tension and hyperalgesia in the segments C_{4-7} or D_{3-9} or D_3–L_1. In diseases of the pleura these symptoms are also present.

In pulmonary tuberculosis the segmental symptoms characteristic of the affected side are less pronounced. This statement (Hansen) has a special bearing on tuberculosis since its unilateral occurrence is rather rare, so that the concept of a unilateral process has but a clinical meaning without a pathologico-anatomical basis. Besides, early disseminations cannot be established by clinical methods; even for the roentgenological detection a certain time must elapse.

The increase of the skin tension usually corresponds to a segment and presents itself as a unilateral or bilateral change according to the lateral or median site of the affected organ. The markedly segmental character of the symptoms can only be explained by the participation of the central nervous system; they are reflex phenomena. The centripetal route of the reflex (Hansen) starts in the affected organ and passes through the visceral nerves and a ganglion of the trunk into the spinal cord. The centrifugal impulses are probably of autonomic origin. They start from the cell groups of the efferent sympathetic lateral column and stand under the continuous action of the afferent impulses from the organs. The segmental relation between skin and viscus corresponds to Head's zones.

The physico-chemical changes caused in the skin by the viscero-cutaneous reflex action have been verified by several observations. It is known that tissue chemistry and other tissue functions may become changed by reflex processes; for example, antibody production may start

in the segmental area of the diseased viscus. In this respect the differences in the result of the tuberculin reaction performed on both sides should be pointed to. Alpern and Tschernikof found biochemical differences between the exudate of cantharides vesicles on the two sides of the body, the strongest exudation arising in the irritated area.

Paul and Végh produced, by application of mustard paper on the corresponding skin segment, a change of the plasma colloids in patients suffering from liver diseases, manifested by a decrease of the euglobulins and an increased capacity of the plasma to form complement. This cuti-visceral reflex could not be elicited by influencing other skin areas nor in healthy persons.

To evaluate our experiments it is necessary to know the vasomotor phenomena of the skin underlying our experiments. The vasomotor mechanism is, owing to its complicated details, hard to explain in particular. Hess found, beside other results, that every change in the local circulation has an effect upon the whole organism, whereby it is influenced and regulated again and again by the higher centres.

The skin effect of the impulse starting from the organ can be shown by an interesting experiment. Wernoe elicited vasoconstriction and fading of the cutaneous pigment by irritating the viscera in codfish and eels. The alteration extended over the area of several segments. The skin zone influenced by segmental irritation was bilateral with the irritation of unpaired organs, and unilateral when a paired organ was acted upon. The phenomenon always appeared on the side of irritation over an area corresponding to the innervation segment of the viscus in question. After crushing the spinal cord and blocking the sympathetic ganglia by nicotine the viscero-cutaneous vasoconstriction reflex could be elicited, though in a mild form; after destruction of the sympathetic trunk the reflex could not be produced at all. Wernoe concluded from these results that the reflex in question was a postganglionary axon reflex. In the reversed experiment, visceral hyperaemia was found after irritating the skin, if the spinal cord was intact. After destruction of the cord a vasoconstriction appeared following the same stimulus. The author concluded that the cuti-visceral reflex of vasodilation is of spinal origin, whereas the cuti-visceral vasoconstriction is an axon reflex.

In addition to these experiments, the results of Starling and Führer and those of Charpey and Schafer deserve to be cited; these authors demonstrated in a lung-heart preparation and in living animals the dilatation of the pulmonary vessels by reflexes. Galeotti, Azzi, Margaria

and I found a close correlation between chest skin and pulmonary vessels, since the presence of pulmonary hyperaemia was shown by dilatation of the skin vessels.

Active hyperaemia of the skin without irritation is never observed in visceral diseases. The irritation of the skin by blistering produces, as shown in our rabbit experiments, vasodilatation in the lungs. Treatment applied on the skin (hot compresses, mustard compresses, cataplasms) acts upon the organs in a similar way.

The results of the rabbit experiments with pneumothorax and blisters, in accord with the statements quoted from the literature, permit the conclusion that the dermato-pulmonary reaction of the rabbit is produced by way of a reflex mechanism. If this conclusion is correct pathologico-histological changes should be present in the reflex arc, that is, in the sympathetic trunk or in the stellate ganglion.

These experiments were performed with rabbits. After depilating an area of the right thorax equal in size to a palm, this area was treated once a day with the blistering agent Rheumapax. After four weeks the rabbits were killed and the sympathetic nerve trunks of both sides were examined histologically.[2] The dissection of the animals was performed immediately after they had been killed.

Figure 1 shows the microscopical picture of the stellate ganglion of the irritated right side, taken from rabbit 5, killed by bleeding.

The specimen was stained with hematoxylin-eosin. The area seen under high-power magnification shows closely arranged ganglion cells; interstitial extravasation and slight cellular infiltration are present. The ganglion cells show a mild shrinkage in the same area. A marked irregularity in the arrangement of cells can be seen. There are staining alterations, the stain being deeper as usual. The left stellate ganglion shows no pathological change.

The rabbit killed after four weeks of blister treatment showed the following histological changes (figure 3): the tissue was stained by the prolonged osmium procedure of Kiss. In the right stellate ganglion the capillaries and small veins are distended with red blood cells. The nervous elements show no significant change.

The changes observed in rabbit 5 are decisively pathological and correspond in every respect to the retrograde alteration produced ex-

[2] The neuromorphological examinations were performed in the Institute for Anatomy of the Pázmány Péter University of Budapest (Director, Dr. F. Kiss). I wish to thank Professor Kiss and his assistant J. Schimmert for their kind and effective help.

FIG. 1

FIG. 2

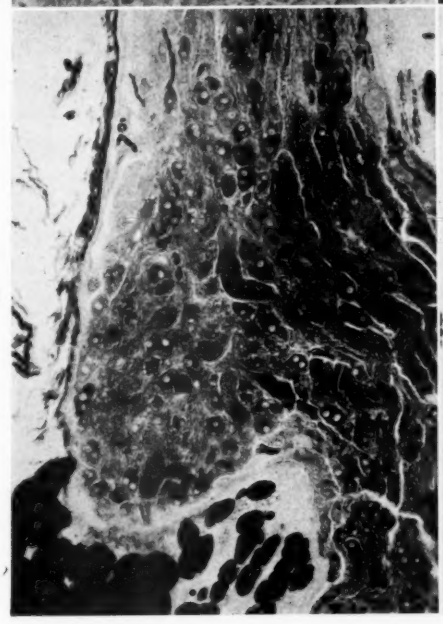

FIG. 3

FIG. 4

FIGS. 1–4

perimentally in the cells of sensitive ganglions that have, according to Kiss, an autonomic function.

The alterations of the cells of the stellate ganglion are assumed to be retrograde changes (figure 5). The axons of a certain cell type, lodged

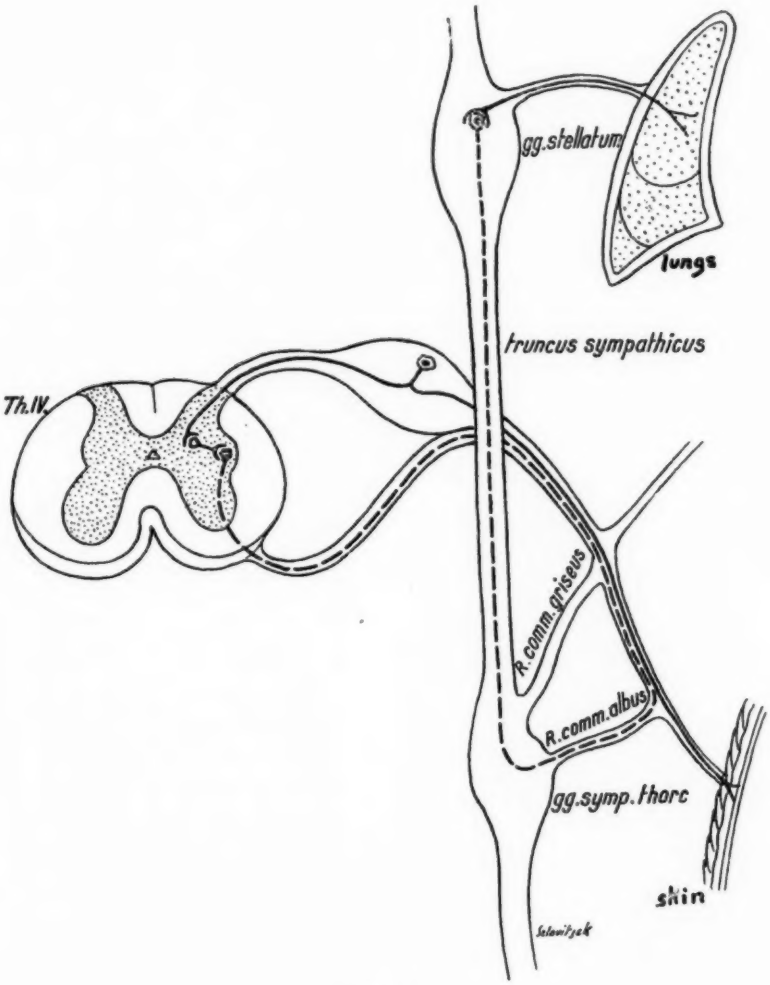

FIG. 5

in the stellate ganglion (relais cell?), pass through the gangliated trunk and surround, by the gray *ramus communicans* of a thoracal segment, some cells of the spinal ganglion with a delicate pericellular network and

carry the irritative or other pathological impulses coming from the skin to the spinal ganglion.

The neurogenic explanation of the pulmonary changes is possible by assuming an autonomic spinal reflex arc. The impulses starting from

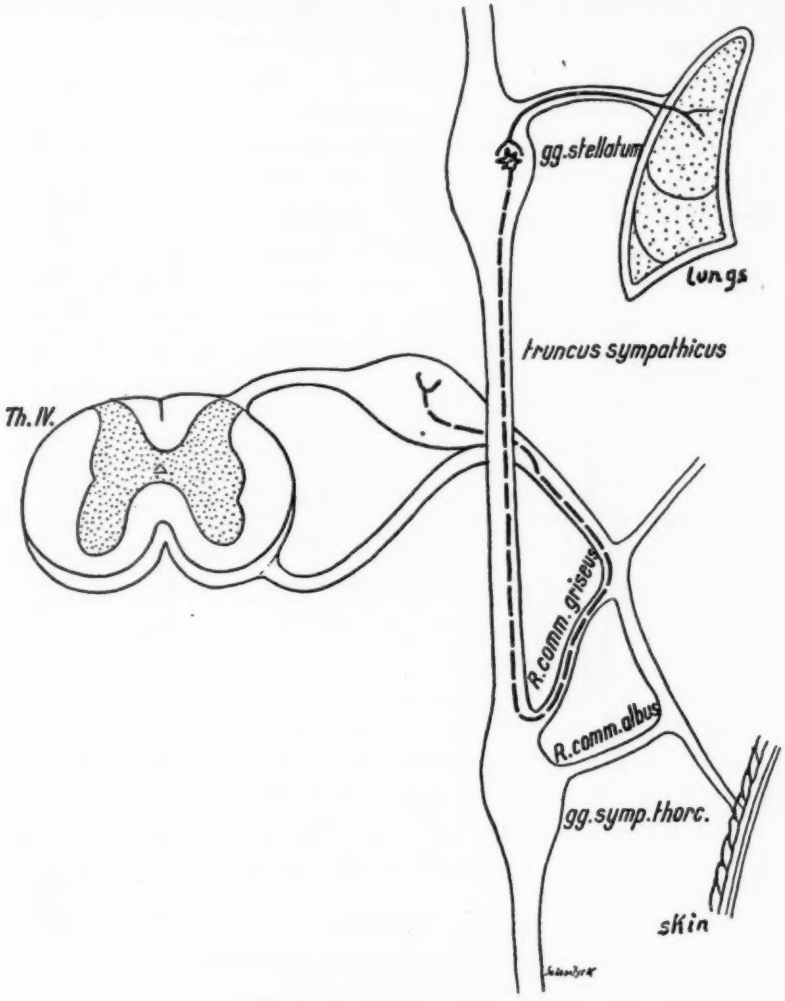

FIG. 6

the skin are carried through the spinal ganglion and the posterior root into the posterior gray column and from there, through a short spinal path, into the sympathetic intermediolateral nucleus from where they pass the anterior root and, through the preganglionary fibres, through

the gray *ramus communicans* and enter the ganglionated trunk in which they ascend up to the stellate ganglion. Here a synapsis takes place to the postganglionic fibres and partly to those ending in the lungs. It is suggestive that the hyperaemia observed in the stellate ganglion is caused by the irritation of the endings of the preganglionic fibres in the stellate ganglion.

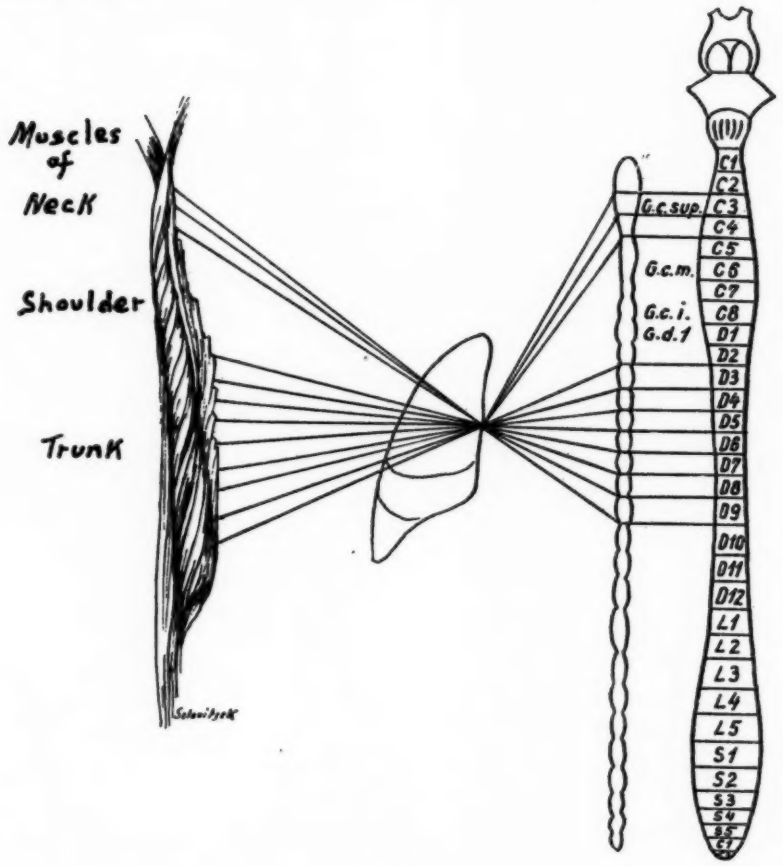

FIG. 7

Figure 7 is a rough representation of the nerve effects starting from and directed to the lungs without a neurologic scheme.

It seems worth while to bring into correlation the pathological changes described above of the stellate ganglion to those in the abdominal sympathetic ganglia produced by other pathological conditions. Abrikossow and Mogolnizcki observed severe inflammatory alterations

representing a sympathico-ganglionitis in diphtheria, scarlet fever, pneumonia and sepsis. The alterations appear either as focal lymphoid cellular infiltrations or as granulomata. The authors pointed out the importance of their findings with special reference to the explanation of the symptoms, particularly the vasomotor disturbances which often give rise to a fatal outcome. Similar changes were found in man in the same infections by Terplan. As to the functional disturbances of the sympathetic system in acute infections, Staemmler ascribed an essential importance to the inflammatory changes of the ganglia. The augmentation of the connective tissue and the lymphoid cell infiltration of the ganglia found with atherosclerosis promotes, in his opinion, the spastic disturbances of the vasomotor function and the production of the atherosclerosis by way of the nerve vessels. Junghans observed, in chronic rheumatism, lymph and plasma cell infiltration in the vessel walls of the ganglia and in the interstitium. Kaiserling reported degenerative processes of the spinal ganglia in acute rheumatic fever. Sunder-Plassmann found in the early stage of appendicitis pathological processes in the terminal plexuses and the ganglion cells adjoining the vessels, and stated that the impaired motility and partly the frequent recurrences were produced by these processes. Fischer and Kaiserling injected serum into the abdominal lymph duct of a rabbit and observed as a sequel an inflammation of the great paravertebral ganglia. This short review favors the suggestion that the sympathetic ganglia, particularly the solar plexus, are the seat of many inflammatory alterations.

According to the results of our experiments, the process obtained was a focal alteration of a ganglion, not as a part of an infectious disease, in which the lesions of the ganglion are caused by blood or lymph dissemination; in our case the pathological change of the stellate ganglion, corresponding to the skin-lung reflex arc, was elicited by an inflammatory reaction of the skin acting as a nerve stimulus.

SUMMARY

1. The dermato-pulmonary reaction induced in rabbits represents to all appearances a reflex process.

2. The mechanism of this reflex has been explained by a reflex arc which is discussed.

3. In the stellate ganglion of the irritated side, vasodilatation, haemorrhages, cellular infiltration and changes of the ganglion cells—a focal ganglionitis—have been found while the corresponding ganglion of the other side was normal.

4. The existence of a reflex arc has been anatomically explained by demonstrating the pathological alterations of the ganglion.

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THE DERMATO-PULMONARY REACTION[1]

III. Influence of the Dermato-Pulmonary Reaction upon Experimental Miliary Tuberculosis

S. PUDER

In our first preliminary paper, unilateral slight pulmonary hyperaemia was reported which had been produced by a unilateral blister treatment of rabbits' chests. The resulting pathological phenomena were termed dermato-pulmonary reaction. There was a report of the inflammatory response of the lung to long acting blistering and the behavior of the dermato-pulmonary reaction in the presence of an artificial pneumothorax. The results indicate that the reaction does not spread by continuity but is produced by a reflex mechanism. These experiments demonstrated the neurogenic origin of the dermato-pulmonary reaction. A direct proof was adduced by the examination of the nerve elements taking part in the reaction. These examinations were reported in a second paper. The stellate ganglion and the gangliated trunk undergo inflammatory changes on the irritated side, supporting the view that the dermato-pulmonary reaction is produced by a reflex mechanism.

In the experiments reported in this paper, acute tuberculosis was produced and the modifications of the acute tuberculous alterations brought about by the dermato-pulmonary reaction were studied.

The animals were divided into three groups. In the first group (control) the animals were infected intravenously with tubercle bacilli. In the second group the animals were infected after an initial blister treatment. In the third group the animals were infected and blistered later.

Experiment 1: One milligram of human tubercle bacilli was injected into the ear vein of the rabbit which was killed fifty-two days later. At autopsy numerous foci, the size of a pinhead, were found in both lungs, particularly in the apices and the upper lobes. In the lower lobes they were scanty, however sometimes confluent. In the liver there were a few tubercles larger than a pinhead. In the slightly congested right lung, tubercles were scattered irregularly, abounding in epithelioid cells and containing sporadic giant cells and surrounded by a lymphoid zone. Some tubercles were confluent. In the centre of most tubercles, caseation was present. The confluent tubercles were more extensively caseated.

[1] From the Dispensary and Department on Pulmonary Tuberculosis of the National Social Insurance Institute of Hungary at Pestszenterzsebet, near Budapest.

Experiment 2: In experiment 2 both sides of the chest were depilated and the right side was blistered with Rheumapax once a day for four weeks. Then 1 mg. of bacilli of human type was injected intravenously and the blistering was continued for another thirty-five days. Thus the skin irritation was maintained for a total of sixty-three days while the tuberculous infection lasted thirty-five days. At autopsy, adhesion of the right apex was seen. Scanty gray tubercles, the size of a pinhead, were scattered through both lungs. There was no striking difference between the two sides. Histologically there was slight congestion in the right upper lobe with occasional small tubercles, caseated in their centres. In some places the tubercles were confluent with extensive ceseation (figure 2). The tubercles of the left lung were fewer in number, irregularly arranged; they seemed to be younger and consisted of heaps of epithelioid cells with a lymphoid zone, but without caseation (figure 2). There were areas with more fully developed tubercles containing small caseated centres yet with less reaction than in those of the opposite side.

In rabbit 3, belonging to experiment 2, no tuberculosis developed. At autopsy no tubercles could be seen. The microscopical picture showed a marked hyperaemia and distended air-cells. Various groups of air-cells were filled with blood. The hyperaemia of the left lung was less pronounced, tubercles could not be seen.

Experiment 3: In experiment 3, the chests of the rabbits were depilated and 1 mg. of human bacilli was injected intravenously. Starting on the twelfth day after the infection, the right side of the chest was blistered once a day over an area of about 4 by 8 cm. for thirty-eight days. The infection lasted fifty days. At autopsy the right lung appeared inflated and congested. In the upper lobe there was confluent tuberculosis, consisting of closely packed foci, from pinhead to pea size, surrounded by haemorrhagic zones. The tuberculosis in the middle and lower lobes was of the same character but less extensive. The left lung was pale and scantily sprinkled with pinhead-sized, gray tubercles. As compared with the right lung of the rabbit of experiment 2, the tubercles in the right lung of this rabbit were more numerous, millet-sized, confluent at several places and cheesy over large areas (figure 3). The tubercles were surrounded by hyperaemia and new and old haemorrhages. There were numerous tubercles in the left lung too. In various places perifocal inflammation and confluence could be observed; the caseation was moderate compared with the right side (figure 4); but the difference is not striking.

The chest of rabbit 5, belonging to experiment 3, was blistered starting on the twelfth day; the treatment lasted, however, only six days because of death eighteen days following the infection. At autopsy

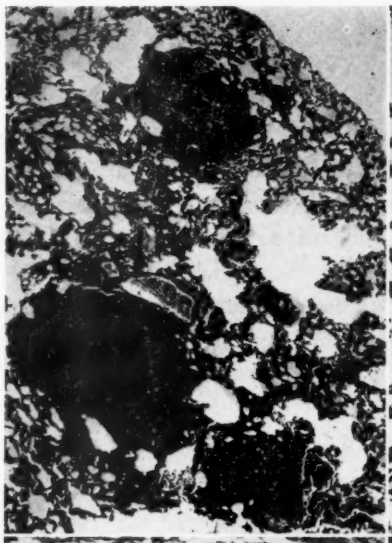

FIG. 1

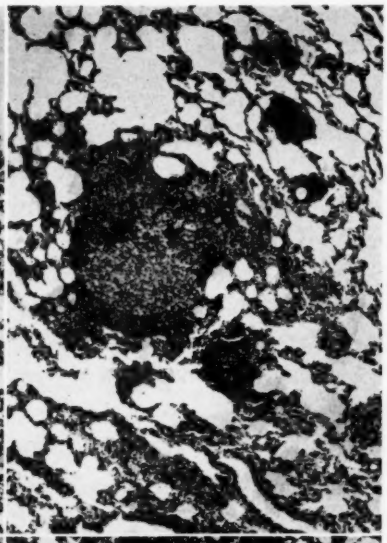

FIG. 2

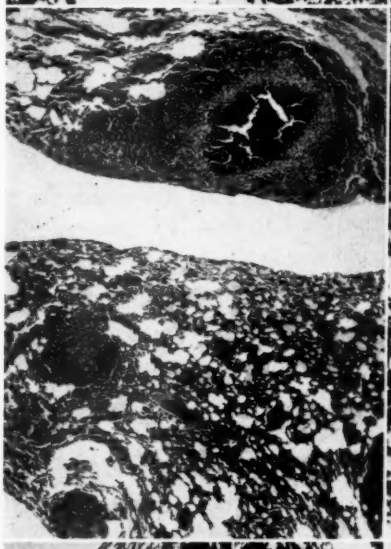

FIG. 3

FIG. 4

FIG. 5

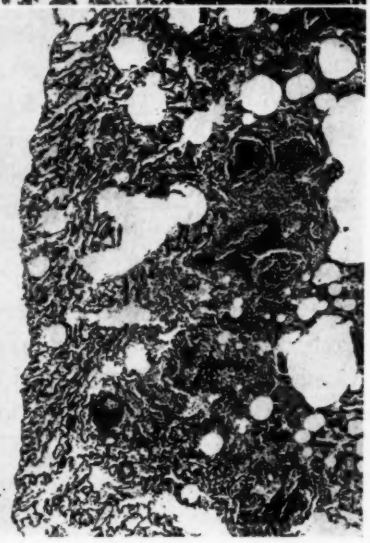

FIG. 6

FIGS. 1–6

grayish white, densely scattered, elevated small tubercles were seen. The lungs were spotted red, the left one less than the right. In the right lung the air-cells were dilated and contained serum, particularly in the subpleural region. There was an early miliary dissemination with tiny foci without caseation. The tubercles lay most densely in the subpleural zone (figure 5). In the left lung, serum was seen in the congested air-cells. There were also early, tiny, noncaseated subpleural tubercles. The histological picture corresponds to an incipient miliary tuberculosis (figure 6).

In experiment 1 which served as control, the infection, lasting fifty-two days, produced a partly confluent cheesy dissemination in both lungs. In experiment 2, rabbit 2 had been blistered for twenty-eight days and was later infected, the infection lasting thirty-five days and the whole experiment sixty-three days. The gross changes showed no great difference between the two lungs, but the microscopical examination showed on the right side extensive caseation of the tubercles while on the left side tubercles were but slightly caseated. In experiment 3, rabbit 4, the blistering was commenced twelve days after the infection and was continued for thirty-eight days, thus giving a fifty-day experiment. The gross changes consisted of densely disseminated tubercles, partly confluent, from pinhead to pea-sized tubercles surrounded with haemorrhagic zones. In the left lung the tubercles were less numerous and non-confluent. The microscopical picture showed in the right lung more extensive changes with more confluent and cheesy tuberculous foci than in rabbit 2. The alteration of the left lung seemed more acute and the caseation was less extensive. The blistering of rabbit 5 which belonged to experiment 3 started (as in rabbit 4) on the twelfth day after infection. The skin irritation lasted, however, only six days because of the death of the animal. Grossly discrete tubercles of the size of a needle-point to a pinhead were seen in both lungs, and both lungs, especially the right one, showed red spots. Microscopically early miliary dissemination was found in both lungs without caseation. The miliary tubercles were specially well marked in the subpleural regions.

These preliminary experiments suggest that the development and progression of acute miliary tuberculosis are promoted by skin irritation in experiment 2 and also in experiment 3 which was arranged in reverse order compared to experiment 2. The stimulus exerted by skin irritation acts on the development of experimental acute miliary tuberculosis as an accelerator. If it should be possible to administer blisters in appropriate doses we might be able not only to stimulate but also to inhibit tuberculous processes. Experiments are under way that may show whether this thought can be realized.

CLINICAL DIAGNOSIS OF PRIMARY CARCINOMA OF THE LUNG[1,2]

SIDNEY DIAMOND

Primary carcinoma of the lung, like most malignant tumors elsewhere in the body, has its greatest incidence in persons in the fifth and sixth decades of life. It is not surprising, therefore, that, with the larger number of World War veterans now approaching the age of fifty, the lesion should be encountered with increasing frequency in the hospitals of the Veterans Administration. In the hospital at Legion, Texas, the diagnosis of primary pulmonary cancer was made clinically and confirmed pathologically in 20 patients during the three-year period from January, 1937 to January, 1940.

The nature of the patient's antecedent history offers the physician little aid in his efforts to establish the diagnosis. Some observers are of the opinion that chronic irritation is a major factor in the production of malignant changes in the walls of the bronchi. However, except for the unexplained high incidence of malignant pulmonary neoplasms among Schneeberg miners with pneumonoconiosis, no definite evidence has been adduced in support of this concept. The actual existence of a significant relationship between the development of cancer of the lung and a previous history of smoking, prolonged exposure to irritating dusts or vapors, or the presence of long-standing bronchopulmonary infection has yet to be shown. Were smoking a factor of any moment, there should have been a marked change in the comparative sex incidence of the lesion in recent years, corresponding to the rapidly growing prevalence of the habit among women. Instead, the predilection of pulmonary carcinoma for men is as pronounced to-day as it was thirty years ago. The influence of irritating dusts has been studied by Vorwald and Karr (1), who present impressive autopsy statistics which indicate that malignant lesions of the lung are no more common in pneumonoconiotic than in nonpneumonoconiotic persons. The belief that tuberculosis, bronchiectasis, asthma

[1] From the Medical Service, Veterans Administration Facility, Legion, Texas.

[2] Published with the permission of the Medical Director, Veterans Administration, who assumes no responsibility for the opinions expressed or the conclusions drawn by the author.

and other respiratory diseases play an important rôle in the evolution of pulmonary cancer has been largely dispelled by the work of Tuttle and Womack (2), Rogers (3), Hruby and Sweany (4), Olson (5) and others. The frequency of the association of carcinoma of the lung and each of the various respiratory diseases appears merely to parallel the relative incidence of the respective diseases themselves. Askanazy (6) has pointed out that influenza often results in a peculiar metaplasia of the bronchial mucosa and has suggested that this alteration in the epithelial cells may be the precursor of a carcinomatous change. The frequency of an influenzal history in patients with pulmonary cancer is not at all striking, however. Koletsky's (7) series of 100 cases included only 2 with a previous history of influenza.

Chronic bronchopulmonary irritation prior to the development of the neoplasm was not particularly marked among our patients at Legion. Eleven of the men smoked; 8 were moderate smokers, 3 heavy smokers. In none of the cases did the patient's occupation or environment involve the continued inhalation of irritating substances. A history of previous respiratory affection was present in 8 patients: 5, all of whom smoked, had a chronic cough; 1 suffered from asthma; 2 had been through a siege of influenza during the epidemic of 1917. The absence of tuberculosis in these 20 patients with pulmonary carcinomata is noteworthy, for the hospital has an active tuberculosis service of more than 200 beds.

A dry, brassy cough is the most frequent early symptom of carcinoma of the lung. It was the first discomfort noticed by the great majority of our patients. When secondary changes develop in the tumor mass or in the atelectatic lung distal to the bronchial obstruction, the patient begins to expectorate varying quantities of sputum. The sputum may be mucoid; it may be blood-tinged; it may be definitely purulent. Frank haemoptysis is a fairly common occurrence. Pain in the chest or shoulder is the second most frequent symptom of pulmonary cancer. It is usually ascribed to involvement of the pleura, but on many occasions the post-mortem findings fail to provide us with a satisfactory explanation for the severity of the discomfort. The pain may be a dull ache or it may be so agonizing that opiates are of little avail in affording relief. The pain is almost invariably persistent; it does not disappear even after the development of intrapleural fluid. In no other pulmonary disease is pain so frequent, so constant and so severe. Dyspnoea is another common symptom. It may be caused by endobronchial obstruction, by metastatic compression of the trachea, bronchi or great vessels, or by the

presence of a pleural or pericardial effusion. Hoarseness resulting from the paralysis of one or both of the recurrent laryngeal nerves is present in many cases. Clubbing of the fingers is often marked. Table 1 shows the relative incidence in our patients of the different symptoms attendant upon intrathoracic changes. In 2 of the patients the initial symptoms were referable to distant metastases.

In the absence of severe infection and extensive metastases, loss of weight and cachexia are not common features in pulmonary carcinoma. The general condition of the patient in most instances remains surprisingly good until the terminal stages of the disease. Only 9 of our patients lost more than ten pounds, and in most of them the loss of weight occurred late in the course of their illness. Elevation of temperature, leucocytosis and evidence of profound anaemia are usually absent in

TABLE 1

Symptoms due to intrathoracic changes in 20 patients with primary carcinoma of lung (initial symptom in 2 patients due to extrathoracic metastasis)

	NUMBER OF PATIENTS	
	Initial symptom	Present before terminal stages
Cough	14	16
Pain in chest or shoulder	2	15
Dyspnoea	1	8
Clubbing of fingers	0	8
Hoarseness	0	7
Frank haemoptysis	1	6

uncomplicated cases. In our group, 6 of the patients ran an irregular fever, 8 had white blood counts in excess of 10,000, and only 2 developed a marked secondary anaemia.

Few patients with carcinoma of the lung survive more than a year or two after the onset of their symptoms. The promptness with which death supervenes in untreated cases varies with the location and rapidity of growth of the neoplasm, the severity of the complications, and the nature of the metastatic involvement. Tuttle and Womack (2) have shown that the average length of life in patients whose tumors arise from major bronchi is much greater than it is in patients whose tumors arise from minor bronchi. In our series the shortest duration was three months, the longest slightly less than three years. The average was eleven months.

There are no physical signs pathognomonic of pulmonary cancer. The most suggestive sign—the only early one—is that of localized narrowing of the bronchial lumen: a unilateral wheeze. This very significant sign was present in 3 of our 20 patients at the time of their admission to the hospital. The wheeze disappears when the bronchial closure becomes complete, however, and as a result the signs elicited in most cases are merely those of the secondary changes, such as atelectasis or abscess formation. At times a large peripherally located tumor mass may itself produce signs of frank consolidation in the involved area. Whereas total bronchial occlusion results in atelectasis, partial occlusion often is accompanied by varying degrees of obstructive emphysema. If the cancer arises at or near the bifurcation of the trachea and impinges upon the orifices of both main stem bronchi, it may give rise to a bilateral wheeze and a symmetrical emphysema, and the condition may be erroneously diagnosed as asthma.

The roentgenographic findings in pulmonary carcinoma fall into two main groups: (*1*) those denoting the presence of the neoplasm itself, and (*2*) those attending the occurrence of secondary changes, the actual tumor mass being too small to be visible. Most cases fall into the second group. Figure 1 is an example of atelectasis of an entire upper lobe following complete closure of the lumen of the corresponding bronchus. The area of diminished illumination is homogeneous and is clearly demarcated from the adjacent pulmonary tissue; the trachea is characteristically displaced toward the affected side and the diaphragmatic leaf is raised. An advanced degree of localized emphysema resulting from partial bronchial occlusion is illustrated in figure 2. A solitary shadow caused by the neoplasm alone is more likely to be present when the carcinoma springs from one of the smaller bronchial radicles and occupies a peripheral portion of the lung. The shadow may be sharply defined, as in figure 3; or its borders may be somewhat irregular, if the tumor invades the surrounding pulmonary parenchyma unevenly, as is the case in figure 4. In a number of patients both the tumor mass and the complicating processes are apparent on the X-ray film. In figure 5 the increase in density in the middle third of the left pulmonic field is partly neoplastic and partly inflammatory in origin. The picture in figure 6 is that of a bronchogenic carcinoma which has become infected and has broken down to form a large bronchiectatic abscess cavity; lipiodol, introduced through an endobronchial catheter, fills part of the cavity. Other roentgenographic changes which may be present in-

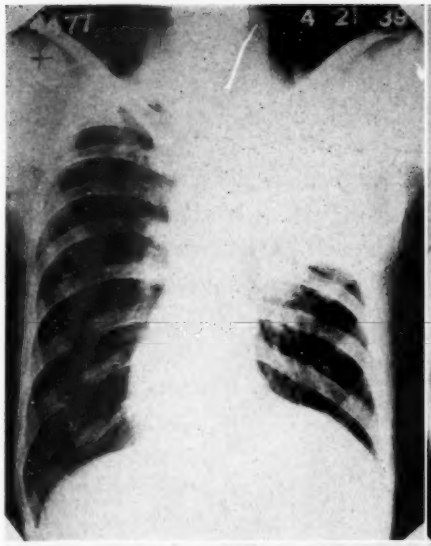

FIG. 1

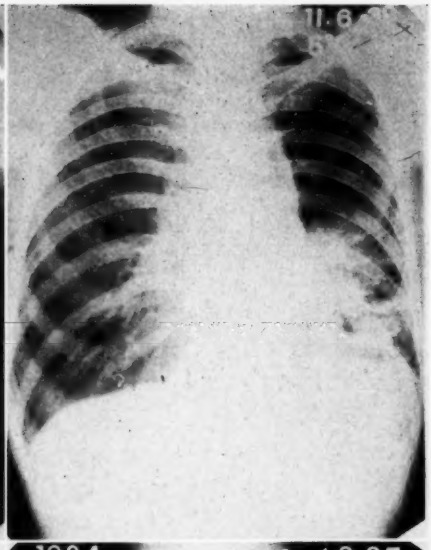

FIG. 2

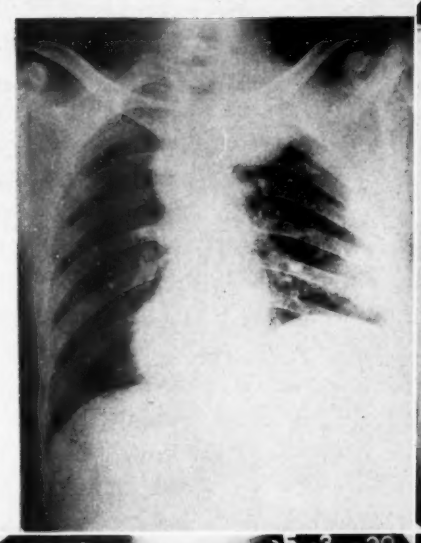

FIG. 3

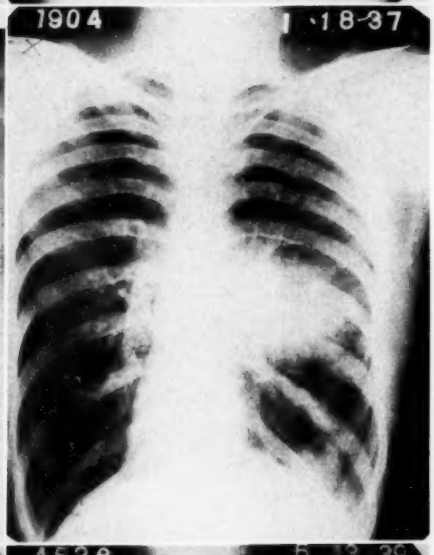

FIG. 4

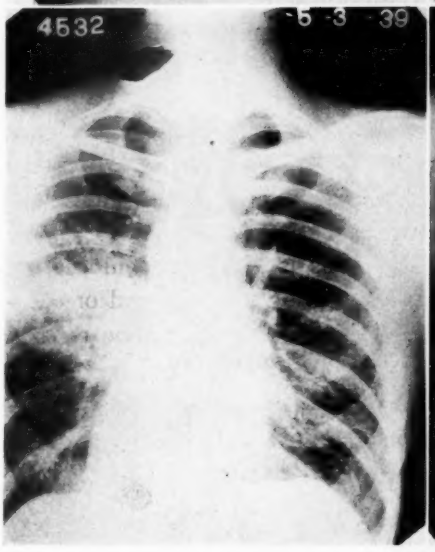

FIG. 5

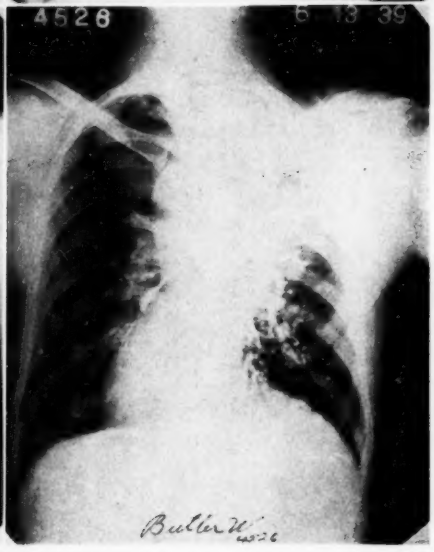

FIG. 6

clude widening of the superior mediastinal shadow from metastatic invasion of the mediastinal structures and elevation of the corresponding dome of the diaphragm from paralysis of the phrenic nerve. The latter phenomenon occurred in 4 of our patients. There may be evidence of destruction of portions of adjacent ribs, but such costal involvement is not common, except in apical tumors.

The complete roentgenographic study of a suspected malignant lesion of the lung may require the use of one or more auxiliary measures, such as the induction of a diagnostic pneumothorax or the endobronchial administration of an opaque contrast medium. A layer of air between the two pleural surfaces will sometimes settle the question of the intrapulmonary status of a shadow when all other means have failed to do so. Iodized oil is often of value in demonstrating stenosis in a bronchus which cannot be seen bronchoscopically. Its use in outlining the surrounding bronchial ramifications will frequently give us a better conception of the precise location and extent of the lesion. Also, the instillation of lipiodol may make the bronchiectatic nature of a cavity evident. The rapid development of a bronchiectatic cavity is strongly indicative of bronchogenic malignancy.

A pleural effusion of obscure aetiology in a person of middle age is highly suggestive of malignant disease of the lung. Intrapleural fluid was present in 6 of our patients; in 2 of them it was the first apparent objective sign. Four effusions were bloody in character, the other 2 clear and straw-colored. In every instance the fluid formed anew soon after being withdrawn. In 2 cases the pleural space was lavaged with oxygen in an effort to promote reëxpansion of the collapsed lung, but the procedure resulted only in the prompt reappearance of the effusion. The tendency of the effusion to be sanguineous and to reaccumulate rapidly after removal is characteristic of pulmonary cancer.

Even though the patient's history and his physical and roentgenographic findings seem to warrant a presumptive diagnosis of carcinoma of the lung, we must be careful to rule out all other diseases, particularly tuberculosis, which may produce a similar picture. In the final analysis, the presumptive diagnosis resulting from the exclusion of a variety of other pulmonary lesions is in itself not sufficient, however. Absolute recognition of the condition must be based on direct microscopical examination of a specimen of tissue from the neoplasm itself. Material for biopsy may be obtained in a number of ways: by bronchoscopy, by thoracoscopy, by thoracotomy, by aspiration of the tumor mass and by the recovery of cancer cells from the patient's sputum.

The positive antemortem diagnosis of pulmonary cancer is made more often by the bronchoscopic removal of a piece of neoplastic tissue than by any other means. This method was employed successfully in 8 out of 16 of our patients whose tracheobronchial trees were directly inspected; in the other 8, the tumor was outside the field of vision afforded by the bronchoscope. Most other investigators have found an even greater percentage of carcinomata accessible for biopsy. Craver (8) is of the opinion that representative specimens of the tumor tissue can be obtained bronchoscopically in approximately 65 per cent of cases. Graham (9) believes that the figure runs as high as 80 per cent. In 3 of our patients the bronchoscopic findings were normal; in each of these the neoplasm originated from a small peripheral bronchus. In the other 13, at least suggestive evidence of the existence of malignant disease was present. This evidence comprised such changes as widening of the carina from involvement of the lymph nodes at the bifurcation of the trachea; marked distortion of the lumen of one of the bronchi; pronounced limitation or even complete absence of the normal cardiorespiratory movements of the carcina or other parts of the bronchial tree. In our small number of cases the tumors themselves had no characteristic appearance. They varied greatly in size, shape, color and the degree of secondary infection. All of them bled readily when touched, however. But even if the nature of the endobronchial lesion should seem obvious upon bronchoscopic examination, the final diagnosis must be made with the microscope. A portion of the neoplasm should always be removed for histological study.

Diagnostic thoracoscopy was performed in 6 of our patients. In 4, the intrapleural space was created by the withdrawal of fluid and its replacement with air, in the other 2, by an artificial pneumothorax which had been induced primarily for the determination of the intrapulmonary character of the lesion. Biopsy of material obtained from pleural nodules confirmed the diagnosis in 2 of the patients. Both of these patients had sanguineous effusions.

Thoracotomy provided the means for our establishing a positive diagnosis in 3 cases. In one case the operation was performed in order to provide external drainage for an acute lung abscess; microscopical examination of a specimen of tissue from the wall of the abscess showed definite evidence of malignant disease. The procedure was a purely diagnostic measure in the other 2 instances; it was employed only after all of our other methods of approach to the neoplasm had been exhausted.

The positive diagnosis of primary carcinoma of the lung was based on the biopsy of a cervical lymph node in one of our patients. This method

of diagnosis is not without its pitfalls, however, and we must caution against overemphasizing its conclusiveness. In a large number of cases the nodes will be filled with nothing but inflammatory tissue, reflecting the secondary changes in the lung rather than the presence of the neoplasm itself. And, even if the node is the seat of a malignant growth, there is always the possibility that this lesion is entirely independent of the disease process in the lung. In our patient the direct relation between the two lesions was demonstrated at autopsy.

No attempt was made in any of our patients to aspirate part of the tumor with a needle inserted through the chest wall. According to Craver and Binkley (10), a large number of pulmonary carcinomata can be diagnosed by this method. For the procedure to be efficacious, however, it is necessary that the pathologist be particularly experienced in this type of biopsy specimen, for he must be willing and able to render a decisive opinion based on the examination of only a few cells. The same is true of the finding of neoplastic cells in the patient's sputum. We examined the sputa of only a few of our patients and were unable to discover cancer cells in any, but Dudgeon (11) has reported the procedure successful in establishing the diagnosis in more than 50 per cent of his cases.

Pathological confirmation of the presumptive clinical diagnosis was not effected in 6 of our patients until the postmortem examination. Two of the patients were too ill to permit diagnostic procedures of an operative nature. The others presented incontrovertible evidence of major extrathoracic metastases, which precluded curative therapy of the pulmonary lesion; surgical measures to confirm a diagnosis of purely academic interest were deemed inadvisable in these cases.

DISCUSSION

Although it may be suspected, the diagnosis of primary carcinoma of the lung cannot be made with assurance the first time the patient is examined. If we are to arrive at the correct diagnosis in the maximum number of cases, we must adopt a painstaking, systematic procedure. A careful history, a thorough physical examination and one or more roentgenograms of the chest constitute the basic step in our approach to the recognition of any pulmonary disease. The data gathered thereby determine the nature of the subsequent work-up. If the findings point to the possibility of malignant disease, the diagnostic program thereafter should comprise two lines of investigation, which are followed simul-

taneously. The first is directed toward the exclusion of other pulmonary diseases and is accomplished by bacteriological and serological studies. The second is directed toward the actual demonstration of malignancy and is accomplished by the removal of a specimen of tumor tissue for microscopical examination. The clinician, like the pathologist, must keep in mind the fundamental pathology of pulmonary carcinoma and its attendant complications; otherwise he is liable to make the error of diagnosing only the complications.

In most cases bronchoscopy is the method of choice for obtaining a biopsy specimen. It has been the policy at Legion to precede the bronchoscopy with a bronchographic study following the administration of iodized oil through a soft rubber endobronchial catheter. Such a preliminary procedure need not be an essential part of the diagnostic program in all instances, however; indeed, in a number of cases it is entirely superfluous. Some peripherally located tumors will be found to be inaccessible bronchoscopically; in such cases the creation of an artificial pneumothorax, for the thoracoscopic removal of a specimen from any pleural seedings which may be present, is indicated. Bronchoscopy may be of little value, too, when the patient has a massive pleural effusion which compresses a main stem bronchus. In cases with considerable intrapleural fluid, therefore, thoracoscopy should be performed first. If thoracoscopy is of no avail, attempts should then be made to induce reëxpansion of the collapsed lung, with consequent reopening of the closed bronchial lumen, so that bronchoscopy may be permitted. If a specimen of tumor tissue cannot be obtained by other means, a thoracotomy should be done. Diagnostic thoracotomy in pulmonary carcinoma is quite comparable to diagnostic laparotomy in abdominal cancer. If we are to treat the patient intelligently, we must first make an accurate diagnosis. And the final diagnosis of carcinoma of the lung can be made only histologically.

A limited number of patients with malignant pulmonary disease can now be cured by lobectomy or pneumonectomy. That number will become progressively larger as we make more and more early diagnoses. Ideally, the patient should be presented for the surgical extirpation of his neoplasm while he is still in good physical condition, before there has been any marked extension of the tumor, before there has been any metastatic spread. Years ago Jackson and Jackson (12) remarked that the bronchoscope afforded the only means of making an early positive diagnosis of malignant disease of the bronchi and lungs. Their state-

ment is still true. Only by early bronchoscopy can we hope to discover a bronchogenic tumor in its incipiency, even before physical and roentgenographic signs have made their appearance. Every adult who has a cough, haemoptysis, thoracic pain or dyspnoea which cannot be adequately explained merits a diagnostic bronchoscopy at an early date. When this fact is universally recognized, the incidence of surgical cure in carcinoma of the lung will be increased.

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BRONCHOMONILIASIS[1]

C. J. KOERTH, J. M. DONALDSON, JR. AND R. G. McCORKLE

Primary bronchomoniliasis was first reported as a clinical entity by Castellani in 1905, as observed in a patient employed as a "tea taster" in Ceylon, India. The first case report published in the United States was made by Boggs and Pincoffs (1) in 1915. The great number of case reports found in the literature since this pioneer work was done indicates the frequency with which this condition is encountered. From his studies of patients with pulmonary disease and examination of the throats of normal individuals, Keiper (2) concluded that 3 per cent of apparently normal individuals harbor monilia organisms in their throat and that 2.93 per cent of pulmonary disease is due to the monilias.

As with other fungus infections, bronchomoniliasis is more common in the tropical and subtropical climates but, masquerading as pulmonary tuberculosis, it undoubtedly occurs in all latitudes as indicated by the wide geographical distribution of the reported cases.

CASE REPORTS

1: S. T. P., a male, age fifty-nine years, farmer, was admitted to the Woodmen of the World Hospital on July 6, 1939, with the chief complaints of productive cough, malaise, loss of weight, strength and appetite, dyspnoea, and night-sweats. In January, 1939 the patient began to tire easily, and noticed he was short of breath. In March, 1939 he had influenza and since then has had a productive cough. Fever appeared in June, 1939 and he consulted his physician who, after physical examination, told the patient that he had pulmonary tuberculosis. The patient had measles, mumps and pertussis when he was a child. He stated that he has had no other illnesses previous to the present onset of malaise and shortness of breath in January, 1939.

Physical examination was negative except for the chest. Impaired resonance with harsh breath sounds was heard from apex to base of both lungs with fine, medium and coarse râles on cough over the same area. The erythrocyte count was 3,700,000, leucocyte count 14,600, haemoglobin (Dare) 76 per cent, color index 1.02, polymorphonuclears 71 per cent, lymphocytes 19 per cent, monocytes 4 per cent, eosinophils 6 per cent, stab-nuclears 7 per cent, seg-

[1] From the Woodmen of the World War Memorial Hospital, San Antonio, Texas.

mented nuclears 64 per cent; sedimentation rate[2] 39 per cent, 60 per cent, 71 per cent; Weltman band 6, Kolmer negative, Kahn negative, agglutination for Malta fever and tularaemia negative, basal metabolic rate −15, smears from the gums were positive for Vincent's spirochetes. Except for a moderate number of pus cells and occasional granular casts the urine was negative. During the patient's stay at the institution 13 direct sputum smears were negative for tubercle bacilli. One specimen was planted on Loewenstein's medium and remained negative. Cultures of the patient's sputum were made on Sabouraud's glucose agar during his stay at the hospital. Five such cultures were negative for fungi, while 8 others showed the presence of monilia. The patient rinsed his mouth with an antiseptic with a pH of 3.6 before expectorating to prevent oral contamination when the specimens were collected for culture. Cultures planted on Sabouraud's glucose agar of secretions taken from the bronchi by means of a bronchoscope and from a laryngeal smear resulted in no growth of monilia. Bronchoscopic examination was done by Dr. R. E. Parrish with the following report given: "The trachea appeared to be normal in the upper portion; in the lower portion and in the common bronchi there was evidence of an inflammatory reaction which was not characteristic of tuberculosis nor of simple bacterial nature. There was very little discharge and the mucous membrane was somewhat red and definitely roughened. There was no glossy or shiny mucous membrane to be seen in the bronchial tree. There was a small amount of rather thick mucoid discharge being expelled from the right lower lobe. A bronchial applicator was passed and a smear was taken from the bronchial tree and planted immediately upon Sabouraud's agar. The appearance of the trachea and bronchi, as previously mentioned, did not fit in either with bronchiectasis or chronic bronchitis. There was no evidence of ulceration but it appeared to be more allied to a tuberculous process than any other bacterial condition. The unusual appearance is prone to make me consider the possibility of a fungus infection or some other rare condition. There was no evidence of a foreign body."

Suspensions of the conidia of the organism isolated from the patient's sputum were made by suspending the forty-eight-hour growth on glucose-agar slants. The suspensions were killed by heating for one hour in a water bath at 56°C. and phenol was then added to preserve it. Agglutination tests were run with dilutions of the patient's serum as follows: 1:10, 1:20, 1:40, 1:80 and 1:160. Agglutination occurred in the dilutions 1:10, 1:20 and 1:40. No agglutination was produced by the serum from a normal control. The organism (figure 1) isolated on many occasions from the sputum of the patient, after the proper precautions had been taken to rule out oral contamination, was studied both as regards its morphological and biochemical characteristics by two dif-

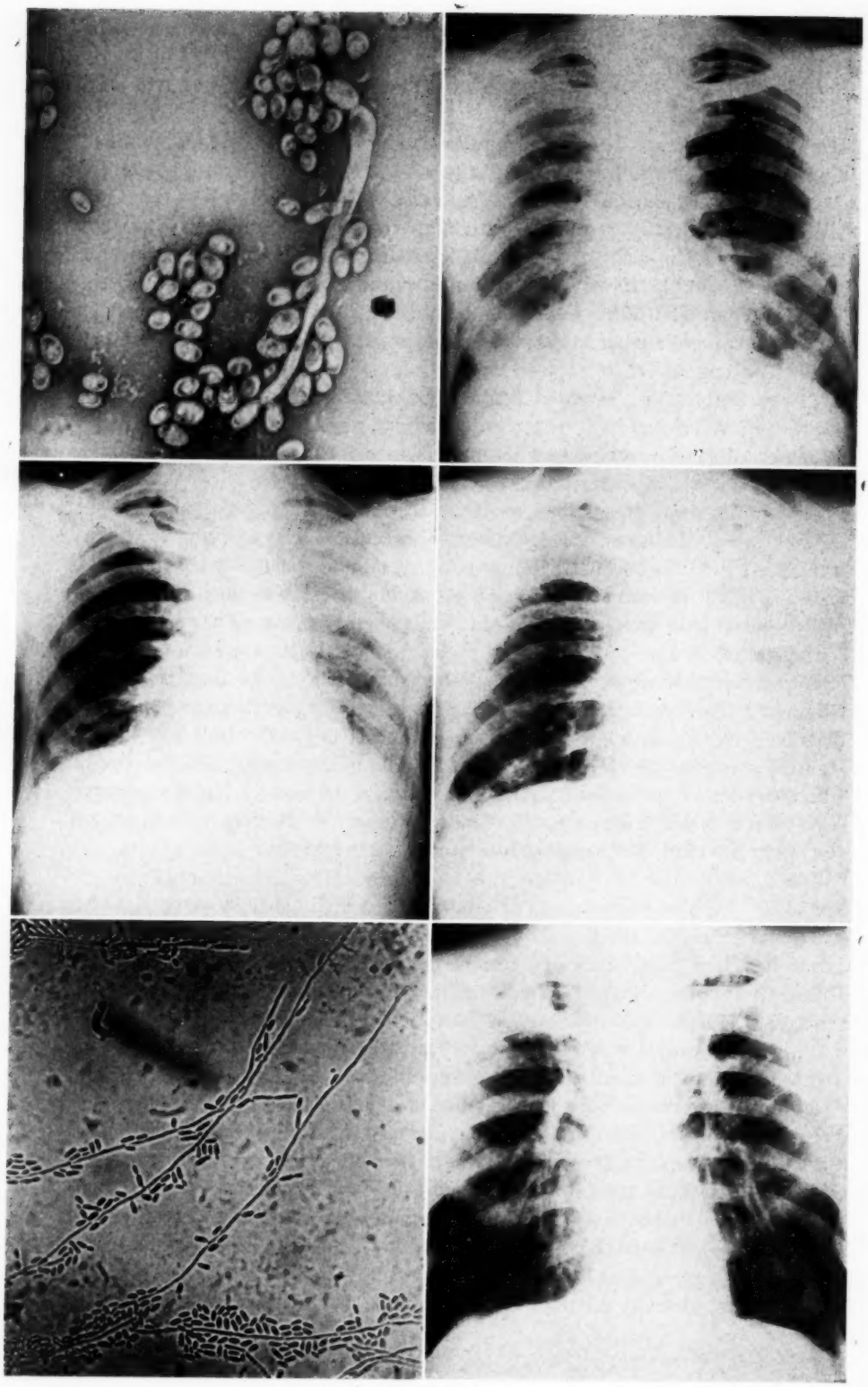
[2] Morris's modification of Westergren's method (33, 34); readings taken one hour, two hours and twenty-four hours.

ferent investigators. The one, using the classification of Castellani, identified the fungus as *Monilia tropicalis*, and the other, using the criteria set forth by Martin *et al.* (3), classified the organism as *Monilia candida*. However, since the latter classification is one in which an attempt is made to place the various monilias into a few groups, there is no discrepancy between the results of these two workers for the latter classification includes *Monilia tropicalis Castellani* in the category of *Monilia candida*. In addition to the studies made upon this organism by other laboratories, the organism was studied in our laboratory with the results noted in tables 1 and 2.

X-ray examination revealed a mottled infiltration throughout the entire right lung which was fairly sharply defined and apparently fibrotic. A band of increased density was present along the course of the fourth rib with an area of infiltration at the extreme base of the left lung (figure 2).

The patient was placed on a strict sanatorium regimen, being allowed out of bed for only bath and toilet. After two weeks his temperature, which had ranged from 99.2° to 99.6°F., dropped to normal and was never above 98.8°F. except on one other occasion during his four months' stay at the hospital. He also began to gain strength and weight. His weight increased from 127 pounds on entrance, to 156. Although the patient's clinical course was not striking, the peculiar manner in which the lesions observed in the roentgenograms (figures 2, 3 and 4) migrated from one area to another, leaving the previously involved area clear, was quite unusual. Another unusual aspect was the extensive pulmonary involvement and the scarcity of symptoms. At the time of discharge his symptoms of cough, night-sweats and dyspnoea had disappeared and he felt so well that he would remain no longer in the hospital and left on October 30, 1939, after almost four months' observation.

2: D. D. W., a white male, age fifty-one years, a merchant, was first admitted to the Woodmen of the World Memorial Hospital on August 4, 1938, at which time his chief complaints were productive cough, fever, loss of weight and strength and loss of appetite. In March, 1928 the patient noticed malaise and fatigue. His family physician told him he had pulmonary tuberculosis. He continued to work for two years and then was examined by another physician who informed the patient that he had no tuberculosis but that his teeth and tonsils were responsible for his symptoms. The tonsils and seven teeth were removed in 1930. His symptoms disappeared and he felt well until July, 1938, when he developed a severe chest cold. He had an X-ray film of the chest taken and he was told that he had pulmonary tuberculosis involving the left lung. One brother had died of pulmonary tuberculosis. The physical examination was essentially negative except for the chest. There was impaired resonance over the right lung from apex to base. The breath sounds were bronchial from the base to the middle of the scapula, posteriorly, and from the apex



FIGS. 1-6

to the third rib, anteriorly. The base of the right lung was hyperresonant. Medium and coarse râles were heard from the level of the spine of the scapula posteriorly to the base and in the lower axilla. Impaired resonance was found over the entire left chest and the breath sounds were harsh over the same area. Bronchial breath sounds were heard over the left apex. The weight was 123 pounds, blood pressure 84/64, temperature 99, pulse 108 and respiration 24. The sputum was mucopurulent and persistently negative for tubercle bacilli by direct smear and concentration. The urine was negative except for a few pus cells. The blood count was normal except for an eosinophilia of 7 per cent. Smears from the teeth and gums were positive for Vincent's spirochetes. The sedimentation rate was 41 per cent, 55 per cent, 66 per cent. The basal metabolic rate was +7. No examination for fungi was made during this admission. X-ray examination showed an infiltration of a proliferative type, producing diffuse fibrosis throughout the right lung field. There were scattered infiltrations with fibrosis throughout the left lung and numerous calcified areas. Lipiodol was injected into the right bronchial tree but no bronchiectasis could be detected on antero-posterior and lateral roentgenograms. After one week of bed-rest the patient's temperature returned to normal and remained so. He gained 17 pounds, his symptoms abated, and his sputum decreased in amount. The patient became homesick and left on October 1, 1938.

The second admission to the Woodmen of the World Hospital was November 14, 1939. The chief complaints were productive cough, fever, loss of weight, strength and appetite. Since the patient left the hospital in October, 1938, he had felt well but his symptoms had gradually returned and he felt run-down. The physical examination was negative except for the chest. Impaired resonance with harsh breath sounds was present over the entire right chest. Bronchial breathing and whispered pectoriloquy were heard at the apex. Impaired resonance was present over the entire left chest and harsh breath

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FIG. 1 (upper left). Case 1. *M. tropicalis* (× 500) showing a hyphal element from which lateral and terminal budding may be observed.

FIG. 2 (upper right). Case 1. July 10, 1939. Entrance X-ray film revealed a mottled infiltration which was apparently fibrotic throughout the right lung. Left lung showed a band of increased density along the course of the fourth rib with an area of infiltration at the base.

FIG. 3 (center left). Case 1. August 18, 1939. The infiltration previously noted throughout the right lung had practically disappeared and there was a marked clouding over the upper half of the left lung field.

FIG. 4 (center right). Case 1. September 22, 1939. The infiltration involving the left lung had increased while the right lung showed practically no change.

FIG. 5 (lower left). Case 2. Ten-day corn-meal-agar slide culture shows long narrow hyphae with oblong conidia.

FIG. 6 (lower right). Case 2. November 14, 1939. This patient's X-ray film shows a moderate infiltration involving the apex and first and second interspaces on both the right and left sides with a cavity on the right above and behind the clavicle.

sounds were heard over the same area. The patient's weight was 125 pounds and the blood pressure was 94/70. The sputum which was mucopurulent was

TABLE 1

	CASE 1	CASE 2	
	Organism from sputum	Organism from sputum	Organism from pharyngeal ulcer
Colony on blood agar	Round, elevated, moist, grayish, ¾ to 1½ mm. in diameter	Circular, elevated, moist, grayish, ½ to 1½ mm. in diameter	Round, elevated, moist, grayish, ½ to 1½ mm. in diameter
Growth on Sabouraud's glucose agar	Abundant creamy moist growth	Abundant whitish rounded growth	Abundant whitish moist growth
Acid glucose broth	Pellicle formation with sediment	Pellicle with heavy granular sediment	Dry surface growth with granular sediment
Gelatin	Inverted pine tree. No liquefaction	Inverted pine tree. No liquefaction	Inverted pine tree. No liquefaction
Staining reaction	Gram positive	Gram positive	Gram positive
Mycelium	2.1–2.7 by 14.2, 27.0 micra	2.3–3.7 by 16.5, 30.0 micra	2.5–3.5 by 12.0, 25.5 micra
Conidia	2.0–3.4 micra in diameter	2.0–3.0 micra in diameter	2.0–3.1 micra in diameter
Slide culture	Long, slender, branching hyphae from which elongated oval shaped conidia were given off. Conidia also showed budding. Near centre of colony conidia were arranged in rows paralleling the hyphae		
Pathogenicity*	Rabbit lost ½ lb. weight. Sacrificed after thirty-five days. Only evidence of gross pathology was a nodule ½ cm. in diameter on surface of liver from which *M. tropicalis* was recovered	Rabbit lost ¾ lb. weight. Sacrificed after twenty-one days. No gross evidence of pathology was found	Rabbit lost ⅞ lb. weight. Was sacrificed after twenty-one days. No gross evidence of pathology was found

* 1.5 million organisms per 100 g. of rabbit weight.

negative for tubercle bacilli on seven direct smears and three concentrations. The urine was negative except for occasional pus cells. The erythrocyte

count was 4,500,000, leucocytes 4,570, polymorphonuclears 44 per cent, lymphocytes 48 per cent, monocytes 8 per cent, no eosinophils, haemoglobin (Dare) 80 per cent, color index 0.88; sedimentation rate 4 per cent, 8 per cent, 48 per cent; Weltman coagulation band 8, the Kahn and Kolmer tests were negative as well as agglutinations for tularaemia and Malta fever. Eleven sputum specimens cultured at various times during the patient's stay were positive for monilia (figure 5). On several different occasions agglutination tests were done with the patient's serum, using the suspension of the organisms cultured from the patient's sputum, and agglutination occurred in dilutions of 1:40 while no agglutination was produced by the serum of a control. Sputum specimens planted on Loewenstein's medium produced no growth of tubercle bacilli. The fungus isolated from the sputum was identified as *Monilia tropicalis*. The morphological and cultural characteristics are given in tables

TABLE 2

Fermentation reactions

	CASE 1	CASE 2	
	Organism from sputum	Organism from sputum	Organism from pharyngeal ulcer
Dextrose	AG	AG	AG
Saccharose	AG	AG	AG
Lactose	0	0	0
Maltose	AG	AG	AG

A—Indicates acid.
G—Indicates gas.
0—Indicates no change.

1 and 2. X-ray film of the chest upon entrance showed moderate infiltrations involving the apex and first and second interspaces on each side. On the right, behind the first rib, just above the clavicle, there was a cavity about 2 cm. in diameter. The infiltrations were chiefly calcified and, except for the cavity, were relatively inactive (figure 6).

The patient was placed upon strict bed-rest and allowed out of bed only for bath and toilet. His symptoms decreased in severity and he gained 24 pounds. He developed a pharyngeal ulcer from which *Monilia tropicalis* was isolated. Intracutaneous injections of an autogenous vaccine (1 cc. containing 50,000 organisms) prepared from the strain of *Monilia tropicalis* isolated from the sputum gave a positive local reaction in the patient but none in controls. Tubercle bacilli were never discovered in the patient's sputum but *Monilia tropicalis* was constantly found and this organism was still present, although in reduced numbers in the sputum, when he left the hospital on May 7, 1940.

DIAGNOSTIC METHODS

Castellani (4) states that to diagnose bronchomoniliasis there must be a continuous absence of tubercle bacilli and the constant presence of monilia in the sputum. The patient must rinse his mouth with sterile saline or some antiseptic before expectorating in order to prevent oral contamination. In this connection Stovall and Bubolz (5) have pointed out that the presence of grayish masses of monilia in the sputum, which correspond to the sulphur granules in actinomycosis, is more or less conclusive proof that the secretions have come from the bronchi. Examination of the sputum by means of a wet preparation may reveal monilia in some cases, but a diagnosis of bronchomoniliasis cannot be made without culturing and studying the organism.

The mere presence of monilia in the sputum is not, of itself, sufficient evidence. The presence of monilia in the sputum after every effort has been made to prevent contamination may be due to one of the following conditions:

(*a*) The monilia may be nonvirulent and not pathogenic but is living saprophytically in the bronchi. An organism with such a saprophytic rôle, when injected into a rabbit intravenously, will be nonvirulent, and intrapulmonary injection will not produce pulmonary lesions.
(*b*) The organism may be virulent but may be a secondary invader and intravenous injection of a rabbit will cause death, but intrapulmonary injection will not cause any localized nodular condition in the lungs.
(*c*) The monilia is the real causative factor of the pulmonary condition. Intrapulmonary injections of this organism will cause both lungs to be studded with a number of white nodules from which the monilia can be recovered.

Schattenberg and Flinn (6), however, found such inconsistent results from the different methods of inoculations other than the intravenous route, that they abandoned all except the intravenous route in their experiments with a strain of *Monilia albicans* from a proven case of bronchomoniliasis.

Martin *et al.* (3) concluded from their experiments that if the ability to produce lesions in the rabbit is taken as evidence of the pathogenicity for man, *Monilia albicans* is the only pathogenic monilia. McKinney (7), on the other hand, found *M. paratropicalis*, *M. psilosis*, *M. tropicalis*, *M. Chalmersi*, *M. enterica* and *M. pseudotropicalis* to be virulent to some degree for laboratory animals. Castellani (8) does not accept the statement that a monilia capable of producing death in a laboratory animal

is necessarily a pathogen causing bronchomoniliasis. It has been his experience that, although monilias isolated from sputum may cause the death of rabbits when injected intravenously or intrapulmonarily, they do not produce the lesion he considers pathognomonic of bronchomoniliasis.

Although pathogenic for man, these yeast-like fungi have been demonstrated on many occasions to be nonpathogenic for laboratory animals (9, 10). Stovall (11) and Castellani (29) concluded from their observations that the virulence of different specimens of the same species of monilia vary as well as that of different species. Castellani (12) has also shown that monilias with the same biochemical properties may differ greatly in their pathogenicity for man and laboratory animals. Warr (13), Steinfield (14), Wallace and Tanner (10), Bakst (15), and Wheelon (16) are of the opinion that the demonstration of virulence of monilias for laboratory animals is not necessary to prove their pathogenicity for man.

The observation of cutaneous reactions following the injection of monilias isolated from cases of monilia infections has prompted numerous investigators to employ this procedure as a diagnostic measure, but there is no unanimity of opinion as to its value. Henrici (17) states that Weiss and Landron compared the skin sensititivity of normal persons with that of cases of sprue to filtrates of cultures of *M. albicans* and *M. psilosis*. A much greater number of cases of sprue gave positive reactions, but one-fourth of the normal controls also reacted to both cultures. Michel (22) injected subcutaneously suspensions of *M. psilosis*, with positive results in cases of sprue and with negative reactions in normal controls. Balog and Grossi (18) used scarification tests, intracutaneous and subcutaneous inoculations in patients with pulmonary moniliasis. When a suspension of *M. pinoyi*, killed by heat, was used, a general nonspecific reaction was obtained. However, they were able to get a positive cutaneous reaction in all these patients when a living unheated suspension of the fungus was used. The 53 controls all gave negative reactions. Steinfield (19) noted a marked cutaneous reaction in many of his bronchomoniliasis patients when they were given injections of vaccine prepared from the infecting organism. Davis and Warren (20) also observed cutaneous reactions in their cases of bronchomoniliasis after intracutaneous injections of vaccines prepared from the corresponding fungus.

Agglutination produced by the serum of a patient with bronchomo-

niliasis as a diagnostic procedure has usually been unsuccessful because of the inability to produce stable suspensions. The agglutination reactions observed in suspensions of the conidia of monilia have been largely discredited because of the occurrence of spontaneous clumping of the organisms. Farah (21) and Michel (22) found the agglutination produced by the blood serum of patients suffering from monilia infections to be of some diagnostic value. Many other investigators such as Bakst, Hazard and Foley (15), Davis and Warren (20), and Hoffstadt and Lingfelter (23), have found agglutination reactions to be of no value as a diagnostic procedure.

Making use of the specific precipitins in the patient's blood serum, many investigators have attempted to diagnose the infection. This procedure has been notably unsuccessful, as concluded by Michel (22). He was able, however, to use the patient's blood serum in complement fixation tests as a diagnostic procedure.

Eosinophilia has been constantly observed in the blood of patients with asthma (19) due to monilia as well as in cases of bronchomoniliasis (15). Steinfield (27) has also shown that an eosinophilia may be produced in the blood and peritoneal exudate of experimental animals by the injection of monilias.

IDENTIFICATION OF THE MONILIAS

Because of the simplicity of the organism monilia, it has been difficult to classify it satisfactorily as to its proper generic position. It is tentatively placed in the group of *Fungi imperfecti* or *Hyphomycetes*. Because of its lack of distinguishing characteristics, it has been impossible to separate the genus into species upon purely morphological characteristics, although various unsuccessful attempts have been made.

The gross morphology of colonies (11) of different species as well as microcultures (3) has been used extensively as a means of identification, but these must be supplemented by cultural characteristics to separate some of the species. An objection that may be raised to the gross morphology, in addition to the similarity observed in different species, is the variation in appearance which may be produced by age (24), reaction and type of culture media, oxygen tension (25) and other factors.

Castellani (4) recognized the plurality of the species and has attempted to classify the monilias according to their ability to ferment different sugars. Besides the varying results observed by different investigators, varying results are often obtained by the same investigators with the same organism at different times. In other words, the organisms de-

velop the ability to ferment sugars which they were unable to ferment when first isolated. Castellani answers this challenge by postulating that the organism should be identified immediately after it is isolated.

Dodge (30) believes fermentation reactions to be quite variable; however, Woolley (31), using the method of Stovall and Bubolz (5), was able to obtain consistent results. Croft and Black (32) found sugar fermentation to be of value in separation of species, but variations occurred which lead them to believe that fermentation reactions must be supplemented by other observations.

Stovall and Bubolz (11) were able to obtain consistent fermentation reactions with monilias isolated from sputum. On the basis of the observed sugar fermentations and morphological studies, they were able to recognize three distinct types of monilias. Martin *et al.* (3) utilize a combination of characteristic macroscopical colony formation, microscopical colony morphology and sugar fermentation to divide the genus monilia into six species.

More complicated procedures for identification of the monilias have been evolved using precipitin tests, agglutination, complement fixation and antibody absorption. These methods have produced varying results with different authors (2, 3, 7, 20, 28).

ROENTGENOGRAMS

Roentgenological studies may be negative or show peribronchial thickening, areas of infiltration, consolidation, fibrosis, pleural thickening or scattered nodules throughout the lung fields. The lesions are chiefly confined to the bases of the lungs (15). According to Warr (13), in primary bronchomoniliasis the apices remain characteristically clear but otherwise the X-ray films may resemble those of pulmonary tuberculosis. Cavitation and pleural fluid may be observed.

Notable exceptions to this characteristic picture of basal involvement are presented in many cases reported in the literature in which apical involvement gave a remarkable resemblance to pulmonary tuberculosis (20).

In other cases the pathological area migrates throughout one or both lungs as in case 1 reported in this communication.

CLINICAL TYPES

Three clinical types of bronchomoniliasis have been described depending upon the severity of the infection. The mild type affects the patient's general condition very little. It produces a slight cough with scanty

mucopurulent sputum; there is no fever. Physical examination of the chest is frequently negative but a few scattered râles may be found. The course of the disease usually extends over several months at the end of which time these cases may go on to the severe type or clear up spontaneously.

The moderately severe type presents the picture of bronchial catarrh with fever, cough and paroxysmal dyspnoea. Blood-streaked sputum may be present and the signs characteristic of chronic bronchitis are found on physical examination. This type of case may show signs of activity for years or go into the severe type.

The severe type resembles pulmonary tuberculosis in its clinical manifestations and frequently in its X-ray picture. Hectic fever, loss of weight, night-sweats, fatigue, chest pains, cough, haemoptysis, dyspnoea, anaemia and emaciation may be present. The sputum is mucopurulent and may be copius or tenacious and hard to raise.

Physical examination of the chest reveals râles, evidence of pleural thickening or pleural exudate or evidence of cavitation and consolidation. The breath sounds may vary from bronchovesicular to bronchial or they may be absent. An occasional pleuritic rub may be discovered. Severe cases are frequently fatal.

Acute cases may occur with a sudden onset and progress rapidly to a fatal termination. Chronic cases usually begin insidiously and progress slowly over a period of years with remissions and exacerbations.

Besides the bronchopulmonary type of moniliasis, tracheobronchitis, lobar pneumonia, bronchial asthma and chronic bronchitis have been reported due to monilia. In some cases the course may resemble pneumonia with an acute onset, rigors and high fever which falls by lysis in from eleven to fourteen days. Sore throat, huskiness and inflamed tonsils may accompany the pulmonary infection.

One case reported by Black and Eddy (24) presented a monilia infection of the lungs, skin and bones.

PATHOLOGY

The gross and microscopical pathology closely resemble that of pulmonary tuberculosis. Consolidation, cavitation, fibrosis and tubercles are found. Microscopical examination (4, 26) of the pulmonary tissue reveals thickening of the alveolar walls and tubercles composed of a caseous centre, surrounded by epithelioid cells, lymphocytes and an occasional giant cell.

Schattenberg and Flinn (6) found that, while the gross pathology was similar, the microscopical pathology differed in animals injected with monilia according to the dosage given and the consequent length of survival. In animals in which the dosage was sufficient to kill the rabbit in from twenty-four to forty-eight hours, the gross lesions resembling tubercles were found microscopically to simulate early abscess formation with necrosis in the centre of the nodule and polymorphonuclear response at the periphery. On the other hand, the lesions produced by smaller doses of organisms showed epithelioid cell proliferation, giant cell formation and peripheral lymphoid cell infiltration.

No lesions have been described which are generally accepted as pathognomonic of bronchomoniliasis.

TREATMENT

Iodides have been found to be quite efficacious in the treatment of bronchomoniliasis. Potassium iodide is given in doses of five drops three times daily and increased as tolerated until thirty drops three times a day are reached. Needless to say, the presence of tuberculosis must be ruled out before iodides are administered. Iodide therapy may well be supplemented by subcutaneous injections of vaccines prepared from cultures of the organism isolated from the patient's sputum.

Tar in the form of *pix liquida*, one gram a day or more, has been used. Thymol by mouth, gentian-violet, and methylene-blue intravenously have also been useful in the treatment of pulmonary moniliasis.

Roentgen therapy has been used in some cases and has been reported to have produced fair results. Insulin has been used to improve the appetite and to obtain a gain in weight, as well as other means to build up the patient's general resistance, not the least of which is rest. Intratracheal and intramuscular injection of lipiodol have been recommended in severe cases.

DISCUSSION

Case 1, whose sputum contained a monilia identified by one investigator as *M. candida* and by another as *M. tropicalis*, presented an unusual roentgenological picture: successive involvement and subsequent resolution in different parts of both lungs.

Case 2 presented the roentgenogram of chronic productive tuberculosis with cavitation, fibrosis and calcification, but tubercle bacilli in the sputum were never demonstrated, while *M. tropicalis* was constantly

present. Still another interesting feature of this case was the development of a pharyngeal ulcer from which *M. tropicalis* was isolated.

A feature common to both our cases was the extent of the pulmonary pathology and the scarcity of symptoms.

Although in case 1 monilia was not obtained in culture of secretions taken from the bronchial tree by means of the bronchoscope on a single occasion, this does not necessarily mean that moniliasis was not present. The fact that the patient's blood serum produced agglutination of the organism while the serum of controls did not, is evidence, if not proof, that the monilia was the causative organism. In case 2 the occurrence of positive cutaneous reactions, while controls showed no reaction to a suspension of the monilia, we believe to be of significance. Pathogenicity for laboratory animals was not demonstrated for the organism isolated from the sputum of either case.

There seems to be little agreement as to the measures necessary to be fulfilled in order that a diagnosis of bronchomoniliasis may be made. Many investigators require the production of what they consider to be pathognomonic lesions by specified means of inoculation of laboratory animals with the organism isolated from the patient's sputum. A host of others contend that the demonstration of pathogenicity of the monilia for laboratory animals is not necessary to prove its virulence for man.

We are inclined to agree with other writers that when all other aetiological factors are ruled out and a monilia is consistently present in the sputum, capable of producing a positive cutaneous reaction in the patient, and suspensions of which are agglutinated by the patient's blood serum, that it is not necessary to demonstrate its pathogenicity for laboratory animals to prove the monilia to be the aetiological agent.

There exists an equal degree of disagreement as to the criteria necessary to identify the species of the monilias.

SUMMARY

Two cases of bronchomoniliasis were presented, in one of which a pharyngeal ulcer developed during the course of the pulmonary disease. The organism isolated from the ulcer was the same as that from the sputum.

The roentgenological appearance, clinical types of the disease, pathology and treatment were also discussed.

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LIPOID PNEUMONIA[1,2]

Report of a Case Simulating Bronchial Carcinoma

J. J. SINGER AND L. J. TRAGERMAN

Oil pneumonia continues to evoke interest because of the frequently unsuspected and unusual manifestations and the always interesting pathological picture it presents. A recent editorial in the Journal of the American Medical Association (1) has again called attention to the dangers of the promiscuous use of nasal oil sprays and the internal administration of various oils. Earlier case reports and reviews have pointed out the frequency of this disease in infancy, old age, debilitated states and in patients suffering from neurological disorders. Clinically significant lesions in otherwise fairly healthy adults have not been reported with such frequency.

We have recently encountered an instance of severe and progressive oil pneumonia in an adult physician, who for many years had taken mineral oil for constipation and in whom the resultant disease-picture masqueraded as pulmonary carcinoma.

CASE REPORT

S. S., white, male physician, aged sixty-two, dated his illness to an anginal attack in 1933. Electrocardiograms and the character of the pain left no doubt in the patient's mind of this condition. Occasionally he would have a spasm of his glottis and would become dyspnoeic; after a few moments he would breathe easily again. He also noticed that swallowing liquids would frequently produce a cough, followed by a spasm of the glottis. He coughed up blood-streaked sputum and every few weeks he developed a temperature of 102°–103°F., and severe cough. After a few days he would cough up thick, purulent sputum which at times had a foul odor.

A roentgen film taken in 1937 showed a rather unusual picture (figure 1). The air content was fair. The bronchial markings throughout the lungs showed fine striations, especially in the upper lobes, resembling silicosis. The hilar shadows were ill defined. The trachea was deviated to the right. Poorly

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[2] This work was done through a grant from the Rose Lampert Graff Foundation.

defined densities which might have been a summation of the bronchial markings were noted, particularly in the right mid-lung field and the left lower lobe. The diaphragms were well rounded and the costophrenic angles were deep.

A diagnosis was made elsewhere of carcinoma of the lung with lymphatic carcinomatosis. However, a close study of this film made the diagnosis of silicosis, fibrosis and pneumonitis probable. The history of the loss of weight, haemoptysis, weakness and pain over the chest warranted a diagnosis of carcinoma. There was no history of exposure to silica dust, as he was a physician all his adult life and as a youth never worked where dust was a factor.

The patient had the following symptoms on January 25, 1938: loss of 66 pounds in three years, loss of sleep, marked dyspnoea, and blood-streaked sputum on two occasions, palpitation and rapid pulse. His temperature was normal but it had been 103°F. the week before. There was marked spasm of the glottis followed by a whoop, especially when the patient would lie down. There was no history of nasal or throat application of oils but the patient frequently swallowed one or two tablespoonfuls of mineral oil for his constipation.

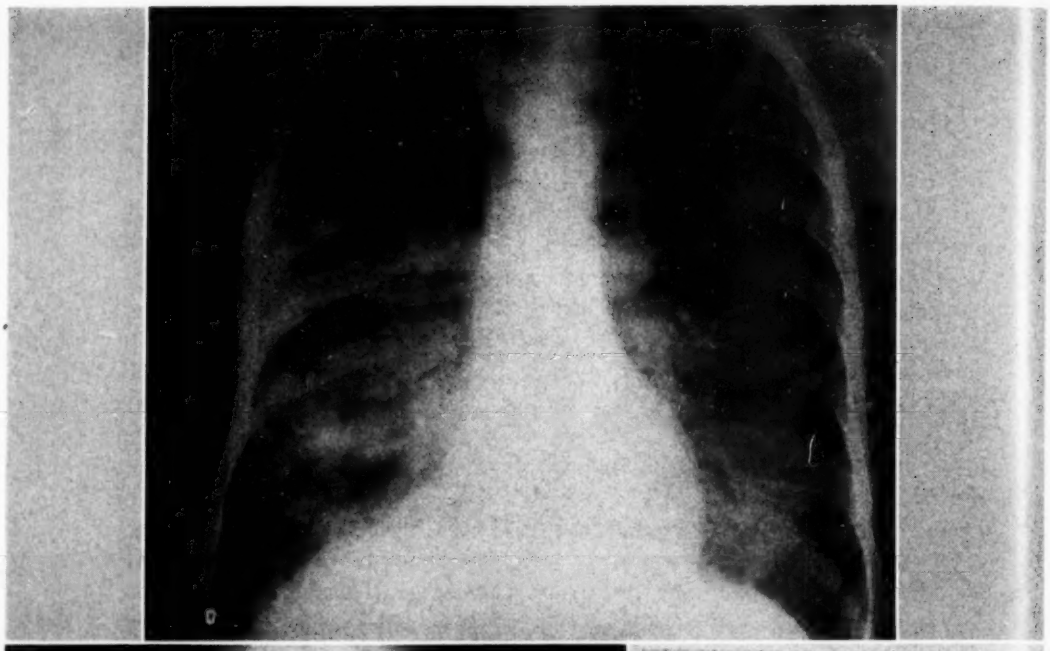
A physical examination on January 25, 1938 revealed the following: He was emaciated and dyspnoeic. The pupils were equal and reacted to light and accommodation. Teeth were fair but worn. The pharynx was congested; the uvula was oedematous. No enlarged cervical lymph nodes were noticed. The chest was rather rigid, with little expansion. The breath sounds were diminished throughout both lungs but compensatory breath sounds were heard in the right base posteriorly. Many râles were heard in the left base. The heart showed no murmurs. The liver was not palpable and the abdomen was otherwise normal. The extremities showed nothing abnormal.

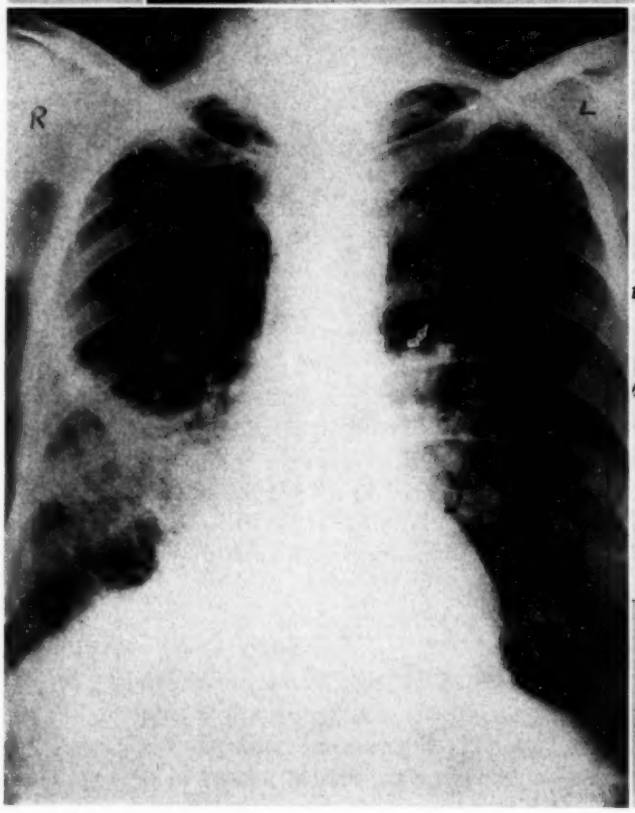
Roentgen films taken on November 8, 1938 (figure 2) showed a marked change from the previous one, in that the fine streaking of the upper lung fields had disappeared. The densities in the right base, however, were increased and in the cardiac shadow one saw a triangular density which usually is evidence of bronchiectatic atelectasis; there was noted compensatory air content in both costophrenic spaces. It was evident from this change that an inflammation had taken place and the residual densities were the result of this inflammation; also that an atelectasis had developed in the left lower lobe.

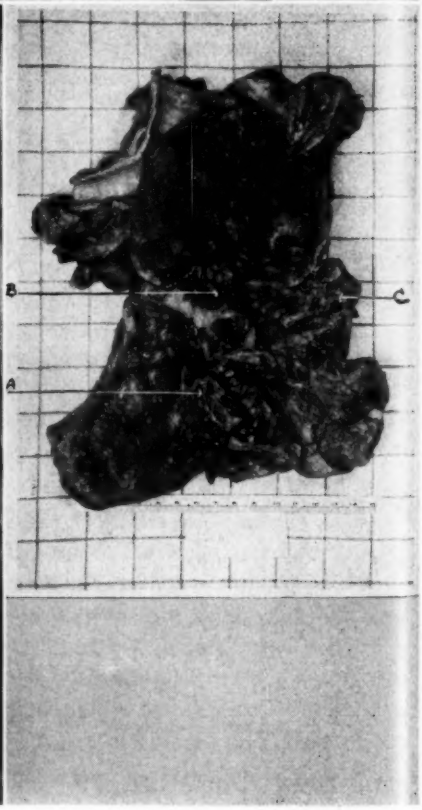
Because of the difficulty in swallowing and the spasm of the glottis a barium study was made of the oesophagus and many films were taken in various positions. No evidence of disease was noted.

The blood picture was of no diagnostic significance; blood pressure was 175/80. The vital capacity was 1,800 cc. The sputum was cultured for fungi and stained for tubercle bacilli; both tests were negative and Wright stain showed occasional eosinophilic leucocytes. It was of interest to note that of the various sputa examined only one specimen showed some oil droplets.

A bronchoscopic examination was suggested but the patient refused to have







FIGS. 1–3

this done, likewise a direct laryngoscopic study. His reason for refusal was that the diagnosis of carcinoma of the lung made originally was so definite that further study was unnecessary and under no circumstances would he permit surgery. Our diagnosis was bronchiectasis, abscesses and emphysema; carcinoma appeared only as a remote possibility.

We did not see the patient from December 13, 1938 to December 31, 1939. During this period he lived in Santa Monica and was treated by Dr. F. Rosenthal. He had considerable ascites and anarsarca and right heart failure secondary to the emphysema and bronchiectasis and abscesses. When the patient was seen on December 31, 1939 he was moribund with temperature of 104°F. He died the following day. The diagnosis before autopsy was multiple abscesses of the lungs, bronchiectasis, bilateral pneumonia.

At autopsy severe chronic passive hyperaemia was present in the viscera, particularly in the liver and spleen. The heart weighed 440 g. and showed severe dilatation of the right side with hypertrophy of the right ventricular wall to a maximum thickening of 1 cm. This, together with considerable dependent oedema, was taken as evidence of death from congestive heart failure. The most important and interesting findings were in the thoracic organs. The following is a summary of this portion of the autopsy protocol:

The left lung weighs 760 g. The visceral pleura is slightly thickened in a few areas. Scattered subpleural emphysematous blebs are present. There are no apical scars. Surfaces made by sectioning are hypercrepitant and feathery in the upper portion of the upper lobe and become progressively firmer toward the base of this lobe. Here there are numerous yellow granular zones which merge into small areas of consolidation. A few of the smaller bronchi near the base of this lobe are dilated; the branches of the pulmonary artery are prominent. The shrunken lower lobe measures 11 cm. from apex to base. It consists largely of thick walled bronchi, some of which dilate in fusiform fashion near the base of the lung. Here several cavities are present on cross section, the largest of which measures 6 cm. in diameter and communicates with the

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FIG. 1 (upper). Roentgenogram of chest taken March 24, 1937. The air content of both lungs is diminished at the bases, while the upper lobes show some thickening and nodular structures. The mass in the left hilar region is suggestive of an enlarged lymph node or tumor.

FIG. 2 (lower left). Roentgenogram of chest taken November 8, 1938. This film shows considerable change from the previous one. In the right base one sees a triangular density, with marked shadows below and a high diaphragm, while the upper lobe is clear. The left lower lobe shows atelectasis while the upper lobe shows clearing as compared with previous films.

FIG. 3 (lower right). Right lung sagittal section. Shows fibrosis of the lower lobe (A) and portions of the upper lobe (B) and middle lobe (C).

bronchus. The intervening parenchyma is firm, gray and grossly airless. The branches of the pulmonary artery are thick walled and many contain old thrombotic material. The peribronchial lymph nodes are enlarged with scattered gray zones.

The right lung weighs 1,180 g. The lower lobe is almost identical in gross appearance to the left lower lobe, including empty cavities at the base, the marked fibrosis of the parenchyma and the presence of old thrombi in many of the branches of pulmonary artery and many of the thickened atheromatous branches of the pulmonary artery (figure 3). The hilar portion of the upper and middle lobes shows parenchymal fibrosis. The upper portion of the upper lobe is emphysematous. Tracheobronchial lymph nodes are enlarged, moderately carbon-pigmented and exude oil droplets on pressure.

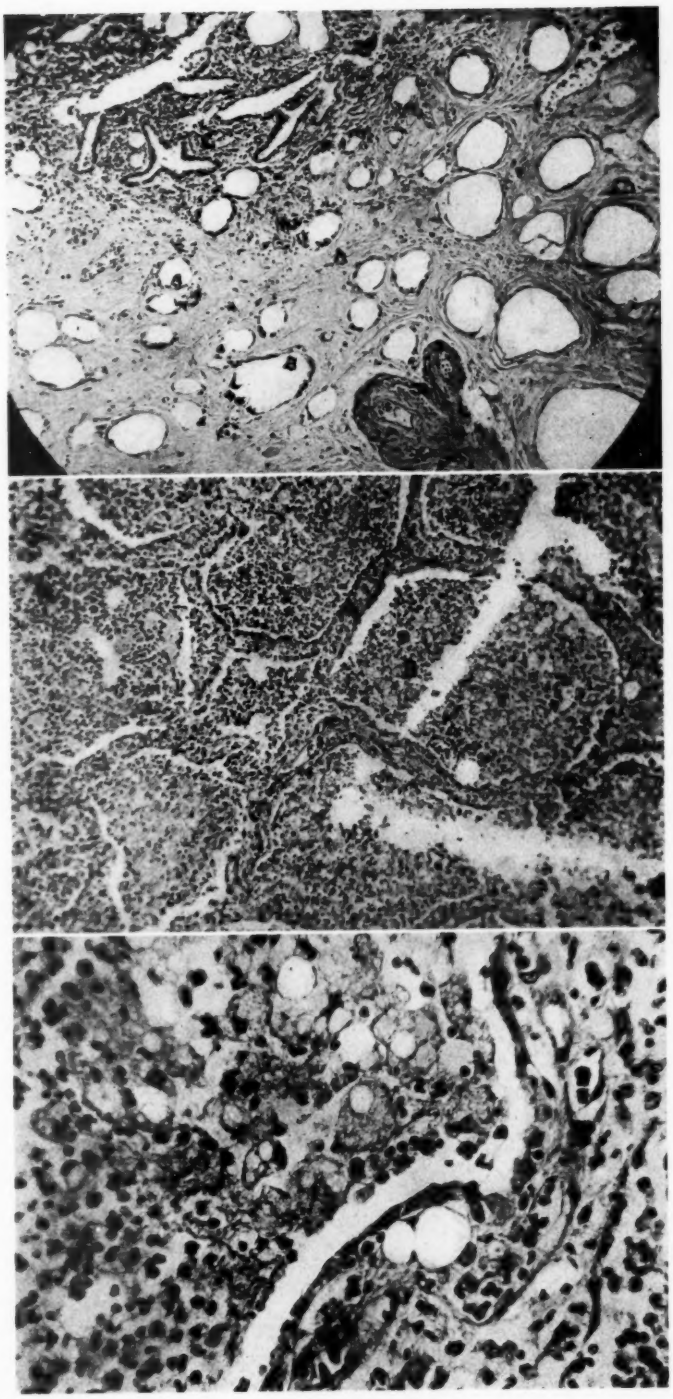
Microscopical examination shows a varied appearance corresponding to the gross changes in the lungs. The most striking changes are in the lower lobes where large portions of parenchyma are completely replaced by dense collagenous connective tissue. Remnants of distorted bronchi and air sacs are occasionally seen. Cystic spaces are present, frequently containing lipoid material (confirmed by sudan-III stain on frozen sections) (figure 4). There is very little inflammatory exudate. In the more granular and consolidated portions of lungs there is fibrinous leucocytic exudation in the air sacs together with large numbers of macrophages, many of which contain fat vacuoles. Alveolar septa are thickened by interstitial accumulations of lipophages and their linings appear prominent (figures 5 and 6). Lipophages are found in scattered numbers in the emphysematous areas near the upper lobe apices. The pulmonary arteries show intimal atheromatous change, medial hypertrophy in the small branches and partial organization of the thrombi in the lower lobes. There is no evidence of primary inflammatory or neoplastic disease of the bronchi. Section of the tracheobronchial lymph nodes shows reticuloendothelial hyperplasia together with intracellular as well as extracellular lipoid deposition.

The anatomical diagnosis was chronic lipoid pneumonia in portions of all lobes, with severe pulmonary fibrosis, bronchiectasis and emphysema; pulmonary arteriosclerosis with thrombosis; chronic *cor pulmonale* with congestive heart failure; terminal bronchopneumonia.

FIG. 4 (upper). Photomicrograph of left lung lower lobe showing intense fibrosis (A), cystic collections of lipoid (B), inflammatory changes about dilated terminal bronchiole (C), and sclerosis of the small pulmonary arteries (D). Low power magnification (× 70).

FIG. 5 (center). Photomicrograph of left lung upper lobe showing thickened alveolar septums with interstitial exudate (A), and intraälveolar exudate (B). In both places there are mononuclear cells containing lipoid material. Low power magnification (× 75).

FIG. 6 (lower). High power magnification (× 320). Same as figure 4.



FIGS. 4–6

Since the autopsy findings revealed extensive lipoid pneumonia, and the only known exposure to oil had been long continued use of mineral oil by mouth for a bowel disturbance, it was thought advisable to attempt extraction and identification of the oil from the lungs. Portions of the right upper and left upper and lower lobes showing varying degrees of involvement were used. This work was done by Mr. G. W. Curtis of the Zeiler, Hammack and Maner Laboratories.

The procedure used for the analysis of the oil is that given by Graef (3). The results, as shown in table 1 are very similar to those obtained by Graef in cases of mineral oil pneumonia. The oil content of these lungs was far in excess of the small amounts of fat normally present. Furthermore the fat normally found in the lungs, as well as abnormally

TABLE 1

PORTION OF LUNG EXAMINED	WET WEIGHT	DRY WEIGHT	TOTAL ETHER-SOLUBLE EXTRACT	PER CENT TOTAL ETHER-SOLUBLE EXTRACT OF DRY WEIGHT	SAPONIFIABLE FRACTION	PER CENT SAPONIFIABLE FRACTION OF TOTAL ETHER-SOLUBLE FRACTION	UNSAPONIFIABLE FRACTION	PER CENT UNSAPONIFIABLE FRACTION OF TOTAL ETHER-SOLUBLE FRACTION	CHOLESTEROL	PER CENT CHOLESTEROL OF TOTAL ETHER-SOLUBLE FRACTION	PER CENT CHOLESTEROL OF UNSAPONIFIABLE FRACTION
	g.	*g.*	*g.*		*g.*		*g.*		*g.*		
Right upper lobe	13	1.35	1.67	123.0		15*	1.017	60			
Left upper lobe	15	1.07	0.24	60.0	0.040	17	0.145	60	0.007	4.8	3.0
Left lower lobe	15	1.07	0.93	86.0	0.075	7	0.78	83	0.003	1.7	0.3

* Estimated.

deposited fats of animal origin, for example cod liver oil, are rich in cholesterol and highly saponifiable. The finding of a low cholesterol content and a high percentage of unsaponifiable material as in our case is further evidence of the deposit of a mineral oil. The physical characteristics of the sample of oil obtained resemble those of liquid petrolatum and it may be inferred that the pulmonary lesion resulted from mineral oil.

From the autopsy findings we are inclined to believe that the picture was largely, if not entirely, due to oil aspiration. Most, and perhaps all, of the changes in the lungs can be explained on the basis of long standing, progressive, active, lipoid pneumonia secondary to the use of mineral oil by mouth for gastrointestinal disturbances for many years. The progressive pulmonary fibrosis with secondary emphysema has eventuated in pulmonary hypertension, complicated by pulmonary arteriosclerosis,

thrombosis, *cor pulmonale* and congestive heart failure. There is some reason to suspect that even the bronchiectatic process in the lower lobe is secondary to pulmonary fibrosis induced by the oil, although an independent chronic bronchitis as a factor cannot be excluded.

Several features of the pathological changes induced by the mineral oil in this patient are worthy of emphasis. The findings in our case conform with the descriptions in the literature of cases of mineral oil pneumonia affecting adults. Graef's observation that a sharp distinction between acute and chronic cases cannot be made is illustrated in our case where all stages of acute and chronic intraälveolar and interstitial reactions are present. This would be expected in a patient who was repeatedly aspirating imperceptible quantities of oil over a long period of time.

The extensive involvement of the regional lymph nodes with oil is an unusual but not undescribed feature in our case. Of greater significance was the unusual deformity of the pulmonary parenchyma. This, together with the compensatory emphysema, we believe was responsible for the right ventricular strain and hypertrophy, upon which was superimposed pulmonary thrombosis. Thus, right heart failure became a complicating and fatal issue in this patient. This is an unusual feature in lipoid pneumonia.

DISCUSSION

Lipoid pneumonia apparently developed early in this patient. The first film shows both the chronic type and the acute form. The latter is shown by the slight thickening of the bronchial tree which later cleared. This condition is not uncommon in infants and when only a small amount of oil had been used. Abscesses of the lung and bronchiectasis followed the acute episodes of pneumonitis and this condition is not distinctly a lipoid condition as other pathological processes. The aetiological factor here is undoubtedly the spasm of the glottis with aspiration of foreign substances in the lung plus regurgitation. The exact cause of the spasm was not ascertained because the patient refused such studies. The use of mineral oils must be condemned especially in infants (6), debilitated patients and those with disturbed swallowing reflexes. The emphysema with bullae developed as a secondary process to the long standing inflammation of the lung. The violent inspiratory efforts during respiration were caused by the spasm of the glottis.

There is no known treatment for this condition, but when the condition is suspected the use of oils should be discontinued.

The terminology of lipoid pneumonia has been discussed by Bishop

(5), who states that the term lipoid pneumonia is probably one of the most frequently employed, although aspirational pneumonia and pneumolipoidosis are also used. Bishop found only 136 cases in the literature and most of these were reported from 1925 to 1938.

When one considers the tremendous amount of mineral oil used throughout the world, this is in reality a small number, but there seems to be no doubt that there are many more cases which have gone unrecognized. Studies such as have been described by Pinkerton, Ikeda, Graef and Bishop (2, 4, 3, 5), and our own case, point the way to correct diagnosis.

In general practice it is recognized that refinements of diagnosis are not available but the urgency of lipoid involvement of the lungs warrants the use of such facilities whether in private practice or in clinics. The presence of fibrosis, bronchiectasis and cystic conditions of the lungs and even malignancies may be coincidental in some cases but the conditions that follow the ingestion of the oil may easily be the source of bronchiectasis and other conditions mentioned above.

In the first roentgen film the markings were such that a definite diagnosis of malignancy was made. The history of dysphagia, with the frequent use of mineral oil by mouth, was suggestive but the tremendous loss of weight and strength and the well being of the patient at other times left some doubt as to the correct diagnosis. Finding of oil in the sputum is not always a positive sign, unless the secretions from the lungs are removed bronchoscopically. This case is reported because of the classical picture of the pathological findings and also to show the necessity of careful history and complete studies in all unusual chest conditions.

CONCLUSIONS

1. A case of severe and progressive lipoid pneumonia in an adult is presented.

2. Long continued use of mineral oil by mouth together with a possible obscure disturbance of the swallowing reflex is thought to be responsible for the development of the lesion.

3. The clinical picture for a long time was dominated by obscure pulmonary symptoms and signs which led to a diagnosis of pulmonary neoplasm.

4. At autopsy the findings were essentially those of lipoid pneumonia, complicated by pulmonary fibrosis and right heart failure; mineral oil was recovered from the lungs.

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MANAGEMENT OF SYPHILIS IN THE TUBERCULOUS PATIENT[1]

PAUL MURPHY[2] AND LEON BROMBERG[3]

The question of the proper management of patients suffering from coexistent tuberculosis and syphilis is one of the most important which we face daily in our clinical work. In fact, if one excludes the degenerative changes of senescence, syphilis constitutes the most serious problem encountered at the Robert Koch Hospital not caused directly or indirectly by the tubercle bacillus.

Somewhat over three years ago it was decided that this challenge of the combined attack by these two diseases could best be met by the close collaboration of a consulting syphilologist with our resident staff. The present report concerns our clinical experience in this field since the appointment of that consultant.

INCIDENCE OF SYPHILIS

Since July 1, 1937 approximately 9 per cent of the adult patients treated for tuberculosis in our hospital have also had syphilis. Although statistics regarding the coexistence of these two diseases vary widely in the published surveys of a number of other institutions, the incidence of syphilis at the Robert Koch Hospital is comparatively high. Using the study made in 1933 by a committee of the National Tuberculosis Association (1) as a basis for statistical comparison, we note that there was an average occurrence of 6.5 per cent of positive serologic tests for syphilis in 20,000 patients from 50 institutions which coöperated in this survey.

The white patients included in the National Tuberculosis Association survey showed an incidence of 4.1 per cent, ours of 5.4 per cent. Their Negroes showed 21 per cent against 17.4 per cent here. The National

[1] Read at the Mississippi Valley Conference on Tuberculosis, Saint Paul, Minnesota, October 4, 1940.

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Social Hygiene Association reviewed the statistics presented by the National Tuberculosis Association survey and concluded that their reported incidence of syphilis was approximately what might be expected in a general population study limited to a similar age and racial groups. It is of interest to analyze more closely our percentages regarding the occurrence of syphilis among 1,444 adults treated for tuberculosis:

Total		
Patients treated (7–1–37 to 9–1–40)	1,444	
Syphilitic	129	— 8.9%
White Patients		
Total number	1,020	
Syphilitics	55	— 5.4%
Males (includes 3 Chinese and 1 Indian)	531	
Syphilitics	35	— 6.6%
Females	489	
Syphilitics	20	— 4.0%
Negro Patients		
Total number	424	
Syphilitics	74	— 17.4%
Males	271	
Syphilitics	49	— 18.0%
Females	153	
Syphilitics	25	— 16.0%
Sex		
Number females treated	642	
Number female syphilitics	45	— 7.0%
Number males treated	802	
Number male syphilitics	84	— 10.4%

The high incidence of syphilis in the Robert Koch Hospital patients is due mainly to the fact that approximately 30 per cent of our 500 beds for adult patients are reserved for Negroes.

DIAGNOSTIC PROBLEMS

The diagnosis of syphilis in a known tuberculous patient may present difficulties. The late lesions of both diseases often show a confusing resemblance to each other. Tertiary changes in the eye, bone, skin and throat may manifest clinical and pathological characteristics of either disease. Pulmonary tuberculosis may cause distortion of the X-ray appearance of the aorta to a perplexing degree. Neighboring pulmonary

disease likewise often obscures the evaluation of cardiac and aortic valvular changes. In our present series of cases we have not encountered and recognized any instance of pulmonary syphilis.

The great majority of our patients suffering from syphilis fell into the category of latent cases. In this group in particular the diagnosis is dependent chiefly on the history and on the serodiagnostic tests. The question of the reliability and accuracy of these tests is, therefore, pertinent and important. According to Stokes (2) the influence of tuberculous disease on the specificity of serodiagnostic tests is disputed. Our institution was one of nine sanatoria which collaborated with the Committee on Evaluation of Serodiagnostic Tests for Syphilis under the leadership of the United States Public Health Service and the National Tuberculosis Association. The conclusion of this critical and comprehensive survey was reported by Parran and Emerson (3) as follows:

> Inasmuch as with the present serological tests for syphilis both typical and atypical false-doubtful and false-positive results are found in sera from tuberculous donors, it is evident that tuberculous toxemia may contribute a confusing factor to syphilis serology. It should not, however, present a major problem in the clinical interpretation of results obtained with carefully conducted serodiagnostic procedures.

We concur fully in this statement. The diagnosis of syphilis is never made at our hospital on the basis of a single unsupported positive serological test. The presence or absence of syphilis can only be established after a painstaking review of the history and physical findings in the individual case, interpreted in the light of confirmed blood and cerebrospinal fluid reports and other relevant laboratory data.

Theoretically, the coexistence of syphilis and tuberculosis in the same patient may materially modify the usual clinical course of either disease. The entire problem of the interrelationship of tuberculosis, syphilis and antisyphilitic treatment has been reviewed and critically studied by Padget and Moore (4). Many expressions of opinion, some diametrically opposed to others, are to be found in the literature. For example, Schlesinger, Orszagh and others quoted by Padget and Moore have stated that active tuberculosis seems to exert a favorable influence on syphilis. Giese and McGovern (5), Habliston and McLane (6) and Gallant (7), after prolonged and careful clinical study, have come to an exactly opposite conclusion.

Experimental work on the subject has been scarce and inconclusive. Padget and Moore (4) quote a Japanese investigator, Ohnawa, who found

that rabbits infected with tuberculosis had a general increase in resistance to syphilis. This worker also found that testicular tuberculosis progressed more rapidly in syphilitic rabbits than in controls. Aronson and Meranze (8) have reported some interesting and significant experiments. They infected rabbits with syphilis and subsequently injected tubercle bacilli into their skins and followed the gross and microscopical tissue reactions, comparing them with the results in nonsyphilitic controls. They found that in the syphilitic rabbits the early histological response to the intracutaneous injection of tubercle bacilli had many of the characteristics of syphilis, but that, as time went on, this tended to change to the typical microscopical picture of tuberculosis. They believe that this phenomenon is based on what is called the *Anamnestische Reaktion*. In other words, the cells of the syphilitic rabbits are so modified by this infection that the subsequent introduction of unrelated organisms (in this case tubercle bacilli) elicits a prompt inflammatory response characteristic of the initial syphilitic infection. Since this fades away in time and is replaced by the usual picture indicative of tuberculosis, it is doubtful if this process plays an important rôle in coexisting human tuberculosis and syphilis.

Lately Aronson and Meranze (9) have published the results of further investigative study which demonstrates the fact that local experimental tuberculosis pursues an identical course in untreated syphilitic rabbits and in syphilitic rabbits treated with treponemicidal doses of arsphenamine.

OBJECTIVES OF TREATMENT

Our primary objective is the improvement of the patient's health and the prolongation of his life; our ultimate goal is his restoration to a useful place in society. The necessity for a high degree of individualization is apparent. In a patient suffering from hopelessly advanced tuberculosis, latent syphilis may be disregarded. Conversely it is gross negligence to leave syphilis untreated in an individual whose tuberculosis gives promise of being controlled. Careful consideration must be given to the problem of which disease constitutes the greater thread to the individual and to society, and therapy must be directed accordingly.

Physicians treating tuberculosis are in grievous error when they assume that associated syphilis is always of secondary importance. It must always be remembered that the late effects of syphilis—notably cardiovascular and cerebrospinal—may be as disastrous, debilitating, and even as fatal as the advanced lesions of tuberculosis. In general it may be

said that pulmonary tuberculosis is more dangerous to contacts than syphilis, but there are numerous and noteworthy exceptions. In dealing with both diseases the therapeutic aim, short of biological cure, is to have the patient live long and usefully in spite of his maladies.

With this in mind, it is often a mistake to let one's therapeutic enthusiasm upset a satisfactory equilibrium which may have already been established in the patient by nature or prior treatment.

CLASSIFICATION OF PATIENTS

Our series consists of 129 patients. All were assiduously studied both as regards syphilis and tuberculosis. All but 13 of these patients had examinations of their cerebrospinal fluid. We insisted on lumbar puncture as a routine procedure unless some definite contraindication existed, such as advanced age or extreme illness.

The race and sex distribution of our patients was as follows:

Negro males	49
White males	32
Negro females	25
White females	20
Chinese males	2
Indian male	1

The average age of these patients was thirty-eight years. This is a little older, by about four or five years, than the average of our general hospital population.

The anatomical extent of tuberculosis in these 129 patients was as follows:

	per cent
Far advanced	73
Moderately advanced	17
Minimal	7
Extrapulmonary	3

It is of interest to compare these percentages with the anatomical classification of our nonsyphilitic patients treated during approximately the same period. (Cases in the primary phase of tuberculous infection were not included in this analysis since they were not represented in the syphilitic group.)

808 Nonsyphilitic Patients

	per cent
Far advanced	66
Moderately advanced	26
Minimal	7
Extrapulmonary	2

According to toxaemia, these patients were classified as follows:

	per cent
Syphilitic	
Group I (slight)	42
Group II (moderate)	40
Group III (severe)	18
Nonsyphilitic	
Group I (slight)	29
Group II (moderate)	45
Group III (severe)	25

DURATION OF DISEASE

Any discussion as to interaction between tuberculosis and syphilis in the same person should consider which disease established itself first. There is very little published information on this point. It is frequently impossible to determine the date of onset of tuberculosis. The same difficulty often arises in getting an accurate history regarding the length of time that syphilis has been present. This is particularly true when dealing with Negroes. However, we made an attempt at this analysis with the following results:

	years
Average duration of tuberculosis	3.5
Average duration of syphilis	18.0

(Based on 70 cases where a fairly definite history of onset was obtained.)

In 109 of our patients we are reasonably sure that syphilis antedated tuberculosis. In 3 instances, tuberculosis definitely was present before syphilis was contracted. In 17 patients the onset of both diseases was believed to be at approximately the same time.

TYPES OF SYPHILITIC INVOLVEMENT

Classifying our 129 patients according to the status of syphilis, we found that they fell into the following categories:

Late latent	86
Early latent	21
Asymptomatic neurosyphilis	6
Paresis	4
Cardiovascular	4
Congenital	4
Tabes dorsalis	3
Gumma of pharynx (healed)	1

Approximately 80 per cent of the above patients had received some sort of antisyphilitic therapy before we saw them. In most cases this

was fragmentary and insufficient. Occasionally it was adequate and in quite a few patients our subsequent treatment was simply the continuation of that already begun elsewhere.

The remainder of the series had received either no treatment at all or merely local applications plus some medicine by mouth at the time they first became aware of their infection. Frequently this treatment had been taken without any professional supervision.

CLINICAL OBSERVATIONS

After a complete study, we decided to administer antisyphilitic therapy to 84 of the 129 patients. Of the remaining 45 patients who received no treatment, 18 were too ill, 6 were considered to have had adequate prior treatment, 7 were uncoöperative and 14 were of advanced age and/or had already achieved an entirely satisfactory equilibrium through natural defense forces.

Some of these patients are still under observation and undoubtedly a few will receive treatment in the future.

Of the 84 patients to whom we have given antisyphilitic therapy, 46 have completed the prescribed course; 22 are still receiving treatment, some of them nearing the end of the course which has been outlined for them. In the remaining 16 patients, the proposed course of treatment was discontinued before completion for the following reasons:

Progression of tuberculosis	7
Left hospital against advice	5
Intolerance to treatment	2
Died	2

PLAN OF TREATMENT

As a result of questionnaires sent to the medical directors of 96 large sanatoria in some 35 different states Guild and Nelson (1) secured data on 25,000 tuberculosis patients and an "excellent cross-section of current practice in dealing with coexisting syphilis and tuberculosis." It is noteworthy that they learned in this survey that one-third of all tuberculosis patients who had syphilis received no antisyphilitic treatment whatever.

The same authors found a wide divergence of opinion on the question of whether or not syphilis should be treated at all in the tuberculous subject. Quoting directly from their authoritative report:

> The weight of which (opinion) seems to be that some form of antisyphilitic treatment should be given, but a few maintain that it is best to disregard the

syphilis unless it be causing clinical symptoms or, as one of them puts it, "We do not treat a positive Wassermann." While some are of the opinion that the tuberculous process would improve little, if any, unless the syphilis is vigorously attacked, the experience of others is that antisyphilitic treatment too often aggravates the tuberculosis and that practically all the treatments now employed in dealing with syphilis are harmful to pulmonary tuberculosis.

Now we feel that the best answer to this confused state of affairs is the classic observation of a French philosopher who said, "No generalization is true, not even this one!"

The question of "syphilis—to treat or not to treat" can only be answered in the individual patient. Three major factors must always be borne in mind in arriving at a decision: (*1*) the age of the patient, (*2*) the extent and toxaemia of the tuberculosis, (*3*) the duration and stage of the syphilis.

These same considerations are also prominent in determining the intensity of antisyphilitic treatment if it is undertaken. Early infectious cases of syphilis must obviously be resolutely treated for the protection of the individual and those in contact with him. The therapeutic risk involved is entirely justifiable. It is likewise advisable to treat the early latent cases of syphilis more intensively than the late latent cases. For example, a young woman of child-bearing age whose tuberculosis is being controlled should have a year of continuous treatment for early latent syphilis if well tolerated. On the other hand, an older woman suffering from late latent syphilis presumably arrested by natural defense forces in the preceding forty years should be left strictly alone.

Each case must be considered on its individual merits. If there is reasonable hope for recovery from tuberculosis and treatment is well tolerated, the patient suffering from coexisting syphilis deserves the benefit of chemotherapy. Our experience has been that, although regular doses of intramuscular medication are well borne, it is advisable to employ moderate dosage of arsenicals intravenously. Our usual practice is not to exceed 0.04 g. of mapharsen, 0.45 g. of neoarsphenamine or 2 g. of tryparsamide in the single dose. Treatment schedules must remain elastic and be modified to suit the tolerance of the patient. A rigid routine of antisyphilitic treatment has no place in the tuberculosis sanatorium.

Unless there are open infectious lesions of syphilis present, every patient started on antisyphilitic therapy should have a preliminary course of intramuscular injections of bismuth salicylate before any arsenical is

given intravenously. The usual adult weekly dosage of bismuth salicylate used is 0.12 g. (2 grains). It is our practice to keep the average case of latent syphilis under continuous moderate treatment for approximately one year, if there are no untoward treatment reactions. The usual patient is given treatment once weekly in overlapping courses of intramuscular injections of bismuth and intravenous injections of arsenicals. Mapharsen (in average dosage of 0.04 g.) is the arsenical of choice. This drug has within the past year practically replaced neoarsphenamine in our therapeutic armory. In equivalent dosage we find mapharsen to be as effective clinically as neoarsphenamine and it is certainly better tolerated. In fact we have experienced no serious treatment reaction to mapharsen.

After the average case of latent syphilis has been treated for one year, therapy is discontinued, regardless of whether or not there has been serologic reversal. Indeed we are convinced that, if the positive blood test remains fixed after such adequate treatment, this is a phenomenon of immunity without practical clinical significance.

The use of iodides has been avoided. Butler (10) has shown in well controlled experiments that iodides hasten the death of tuberculous guinea pigs. Many clinicians believe that iodides are dangerous because of their "softening effect" on reparative fibrous tissue. It has been frequently observed that the use of iodides will cause the appearance of tubercle bacilli in previously negative sputum. Ornstein (11) objects to the administration of potassium iodide for another valid reason. He does not seem to fear its effect on encapsulated tuberculosis, but he is afraid of bronchogenic spread because potassium iodide increases the sputum and renders it less viscid.

Our experience with oral bismuth (Sobisminol) has been too limited to warrant any conclusions.

Patients suffering from neurosyphilis in our series have received bismuth and tryparsamide for prolonged periods of time, depending on their clinical response and the behavior of the cerebrospinal fluid. We have not used fever therapy in these cases because of our belief that such a procedure is dangerous in the presence of active tuberculosis.

Whenever it was found that a patient was intolerant to intravenous medication, treatment was carried on with weekly intramuscular injections of bismuth salicylate only. This latter drug was almost universally well tolerated. A regimen of bismuth only was also advised for patients in whom it was thought that antisyphilitic treatment was desirable but who were too toxaemic for intravenous therapy.

Most clinicians advise deferring all antisyphilitic treatment until the tuberculous patient is relatively nontoxaemic. With few exceptions, we have followed this plan. In several patients we have given the usual treatment in spite of a continuous fever up to 100°F., or over, without apparent mishap. Admittedly this was ill-advised because these particular patients gave slight promise of recovery from tuberculosis. However, this was a useful experience from the standpoint of clinical investigation because it suggests that conservative antisyphilitic treatment might be given with safety to febrile patients. For purpose of observation also we have administered bismuth salicylate intramuscularly to syphilitic patients who were extremely ill from tuberculosis. We found that the drug was well tolerated and did not hasten the decline from pulmonary tuberculosis.

RESPONSE TO THERAPY

Of the 46 patients on whom we have completed treatment, 40 were latent syphilitics. The response to treatment as evidenced by the laboratory reports was as follows: Out of a group of 29 patients whose syphilitic infection was classified as late latent, 11 showed a reversal of the blood test to negative, and there was a significant reduction in degree of positivity in the blood tests of 6 additional patients.

Seven of 11 cases classified as early latent syphilis showed a reversal of blood tests from positive to negative.

Of the 2 paretics, one rather mild case showed considerable clinical gain and improved (though she did not become negative) spinal fluid findings while her tuberculosis became arrested. The other patient had been seriously demented, but was intensively treated in a mental hospital before he was transferred to us. He was sane and had already achieved a reversal of his spinal fluid before we undertook continued chemotherapy. His pulmonary tuberculosis became arrested and he was discharged.

In one case of asymptomatic neurosyphilis, the blood Kahn and Wassermann remained fixed in positivity, but the previously positive cerebrospinal fluid was reduced to negative, coincident with clinical betterment.

One patient suffering from tabes dorsalis was relieved of many of his distressing symptoms, without change in the laboratory reports.

In one patient who showed tertiary syphilitic change (healed gumma of the pharynx), the blood Wassermann became negative; the Kahn test has remained positive.

A single patient with congenital syphilis, whom we have considered adequately treated, has shown no change.

It is noteworthy that the response to therapy in these 46 patients was essentially the same as might be expected in a comparable group of non-tuberculous individuals receiving similar treatment.

REACTIONS TO TREATMENT

The reactions encountered with 2,421 injections of bismuth, 802 of neoarsphenamine, 356 of tryparsamide and 330 of mapharsen have in general not been serious. The majority of reactions consisted of transient nausea and vomiting after intravenous injections of arsenicals. If there was gastrointestinal reaction or other evidence of intolerance on repeated occasions, intravenous arsenicals were discontinued. Two patients had chills and fever after neoarsphenamine; one after tryparsamide. Three individuals suffered a mild arsenical dermatitis which cleared up spontaneously after discontinuance of the offending drug. Out of 11 patients receiving tryparsamide, 3 complained of mild visual symptoms which warranted stopping the drug. There was no diminution in their visual acuity.

As previously stated, bismuth administered intramuscularly gave practically no trouble except for a few cases of gingivitis. Very rarely a patient complained of a mild arthralgia or slight gastrointestinal distress. Occasionally a trace of albumin and a few casts appeared in the urine. A brief respite from the drug or diminution of dosage took care of these mild complications in every instance, except one case of gingivitis in which treatment was discontinued. Only one injection of bismuth provoked a local reaction at the site of injection.

EFFECT OF ANTISYPHILITIC TREATMENT ON THE COURSE OF TUBERCULOSIS

The effect of antisyphilitic treatment on tuberculosis is very difficult to evaluate. When general improvement occurs, as it did in the great majority of the patients comprising the present study, many other factors, such as bed-rest, collapse therapy, etc., have been operating at the same time. Conversely, if the patient becomes worse after treatment, one always wonders if this eventuality might not have happened anyway. By and large, in all of our syphilitic patients, both treated and untreated, the tuberculosis has pursued the course one would expect it to follow if syphilis and antisyphilitic treatment had not been in the picture.

There were 3 notable exceptions to this general statement. Out of our 84 treated cases, these 3 cases deserve brief individual review:

1: One man had a flare-up of previously quiescent cervical nodes toward the end of his course. At the same time his pulmonary tuberculosis went on to

arrest, so it is likely that this was a coincidence and not an unfavorable effect from antisyphilitic treatment.

2: One elderly man had a chill and fever forty-eight hours after his first dose of neoarsphenamine and died within six days of an acute spread of tuberculosis. The injection itself, which was given after five previous intramuscular injections of bismuth, was uneventful. He was an F.A.II when treatment was started. We doubt if neoarsphenamine had anything to do with his flare-up, but it was poor judgment to have given it in view of his age and clinical status.

3: A young female developed high fever three days after her second neoarsphenamine injection and developed an acute spread. In this case also, the intravenous injection itself, given after four previous doses of bismuth, caused no immediate disturbance.

It cannot be denied that in each of these last 2 cases the administration of neoarsphenamine may have been instrumental in causing the flare-up, but surely we often see the same sort of recrudescence in pulmonary tuberculosis without antisyphilitic treatment.

In further consideration of the effect of one disease upon the other it is of interest to analyze the following table, in which we have compared the status of tuberculosis in 76 syphilitic patients discharged from the Robert Koch Hospital since July, 1937 with 888 nonsyphilitic tuberculous patients in similar age groups who have also left the institution during this same period of time.

	76 SYPHILITIC PATIENTS	888 NONSYPHILITIC PATIENTS
	per cent	*per cent*
Arrested	30	29
Apparently arrested	0	4
Quiescent	15	14
Improved	8	14
Unimproved	12	10
Dead	35	29

The patients chosen for antisyphilitic treatment obviously constituted a select group from the viewpoint of the prognosis of their tuberculosis. We have no control group among our nonsyphilitic tuberculosis cases for comparison. It seems worthy of note, however, that of the 46 cases on whom antisyphilitic treatment was completed, 27 have been discharged as follows: arrested 16; quiescent 7; dead 4. Of the 19 who are still hospitalized to date we consider 15 improved and 4 unimproved.

It would appear from a study of our data that the association of tuberculosis and syphilis does not materially alter the prognosis of the tuber-

culosis. Furthermore, we feel no light has been shed on any possible effect tuberculosis may exert on coexisting syphilis.

SUMMARY

1. The proper management of syphilis in the tuberculous individual calls for the close coöperation of specialists skilled in both diseases.

2. Syphilis can be treated safely and effectively in tuberculous patients if each case is considered on an individual basis and reasonable judgment is used.

3. The clinical experience of the authors during the past three years at the Robert Koch Hospital has been reviewed and discussed.

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THE DUALISTIC CONCEPT OF PHTHISIS

ISRAEL RAPPAPORT[1]

In this communication I attempt a rapid backward glance at the famous dispute of a century ago between the schools of Laennec and Virchow. It is my purpose to show that the dualistic concept of phthisis viewed through our present knowledge of tuberculosis appears in a historical perspective which is not only new but is also of considerable clinical interest even now.

In the light of the recent observations on the high incidence of bronchial involvement in pulmonary tuberculosis, we may now better appreciate the rôle attributed by the dualists to bronchial tuberculosis as a basis of distinction between the two types of phthisis. Again in the light of recent experience on the changing trends of tuberculosis associated with the shift in its epidemiology, it becomes possible to explain, at least in part, the different interpretations of Laennec and Virchow by inherent variations in the autopsy materials studied by them.

BRONCHIAL TUBERCULOSIS AND THE DUALISTIC CONCEPT

Since bronchial tuberculosis has recently been rediscovered by the clinicians, it would seem timely to remind ourselves that its first recognition by pathologists served to confirm the concept of the dualism of phthisis. Outstanding pathologists of the generations past not only recognized bronchial tuberculosis and reported it at length, but emphasized its rôle in the characteristic mode of spread of the tuberculous process in the lungs. That the clinicians failed to recognize the clinical phenomena of bronchial tuberculosis is not as surprising as is the fact that they failed to pay proper attention to such complete and convincing descriptions of the morphology of bronchial tuberculosis as for example the following: (Reference: von Niemeyer, Felix: Clinical Lectures on Pulmonary Phthisis, translated by J. L. Parke, New York, 1868, pp. 7–8.)

It is only in a comparatively small number of cases, in which tubercles are met with in the lungs in connection with the products of chronic pneumonias,

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that we can in an unprejudiced examination of the post-mortem appearances, arrive at the conclusion which corresponds to the prevailing views concerning the relation of tuberculosis of the lungs to phthisis, namely, that the development of tubercle has preceded the pneumonic processes, and that the existing cavities are due in part to the softening and emptying out of tubercular conglomerations, and have been gradually enlarged by the softening and throwing off of tubercles, which have continued to be formed in their walls. In this form of phthisis, which should alone be called tubercular, it appears, as Virchow has first shown, that the development of the tubercles starts, as a rule, from the bronchial mucous membrane. Here we often see, even in the trachea and the large bronchi, granulated patches, which consist of innumerable miliary tubercles, or ulcerations with the appearances of the primary and secondary tubercular ulcerations of Rokitansky, but we find moreover in these cases in the smaller bronchi, mingled with the appearances of a purulent catarrh, small whitish and yellow granulations, and we can convince ourselves, by sections made in the right direction, that the development of tubercle has spread from the bronchus to its lateral and terminal alveoli. (See Luschka, Anatomie des Menschen, 1. Band, page 309.)

It is quite obvious that not only were Virchow and his school fully aware of the frequency of the involvement of the bronchi in pulmonary tuberculosis but they in fact considered it a distinct pathognomonic feature of "tubercular phthisis" as against "pneumonic phthisis." Niemeyer's description, quoted above, of "tubercular phthisis" characterized by bronchogenic origin and progressive extension by the same route, is as faithful a picture of what we now call "bronchogenic phthisis" as could be given even to-day. The fact that bronchial tuberculosis thus formed one of the bases upon which rested the old dualistic concept of phthisis is not the only interesting aspect of the history of this dispute.

BENIGN EXUDATIVE PHTHISIS—NOW AND THEN

Speaking of "pneumonic phthisis" Niemeyer includes the following: (Ibid., p. 16.)

None can deny the fact that in certain cases more or less extensive condensation of the lungs of phthisical patients disappear entirely.

This sounds indeed like "benign exudative pulmonary tuberculosis" which some workers to-day believe to have discovered anew. However, as regards the prognosis of these, Niemeyer was more cautious as shown at another place where he says: (Ibid., p. 94.)

These catarrhal infiltrations of an acute origin sometimes undergo complete resolution, but it happens much more frequently that the infiltrated tissue undergoes a caseous metamorphosis, and becomes in a short time disintegrated. Most cases of galloping phthisis, in which, within a few weeks, extensive destruction of the lungs occurs, and the patients lose flesh rapidly, with violent fever, and succumb, originate in the invasion of the alveoli of large portions of the lung by an acute catarrh, and can be designated as the termination of an acute or subacute catarrhal pneumonia in "*phthisis florida*".

Again we may say that no more faithful description could be given, even to-day, of what is now recognized as exudative tuberculosis of the lungs.

TUBERCULAR VERSUS PNEUMONIC PHTHISIS; OR NODULAR VERSUS INFILTRATIVE TUBERCULOSIS

That Virchow and his school of dualists were fully aware of the frequent transitions between the two forms is, of course, obvious. Indeed this is just what was expressed in that famous saying "The greatest danger for most phthisical patients is that they may become tuberculous." (Niemeyer, p. 19.) This is often quoted against them with ridicule, which I cannot help feeling springs from lack of appreciation of the issues involved in their true historical perspective. My interpretation of this saying will be better appreciated after a few points of the fundamental issues have been elucidated.

It is not generally realized that both camps were right in some and wrong in other aspects of the great issues over which they fought. Indeed, in retrospect, now it is not easy to decide which side was more right than wrong.

With the intuition of true genius, Laennec recognized in caseation the essence of tuberculosis. It is on this intuitive insight that his concept of the unity of tuberculosis rested. From the strictly morphological point of view of his time it was hardly based upon a sound foundation until Koch discovered the aetiological factor common to both reaction forms. Furthermore, for the sake of his monistic concept, Laennec threw in the infiltrative lesions with nodular tubercles and, as a follower of Bayle, he considered both as neoplastic structures.

Brilliant morphological observations enabled Virchow to recognize and insist upon the inflammatory origin of infiltrative (pneumonic) phthisis. From the morphological point of view this seemed a sound enough basis for his school to separate the latter from nodular tubercles. The sound-

ness of this must be conceded even now if we consider that the common denominator, the aetiological agent, had not been discovered then. In the zeal of their dualistic concept, Virchow and his school overlooked or misinterpreted the true significance of caseation as a most prominent feature of infiltrative as well as of nodular phthisis. Finally, we must not lose sight of the fact that in the last analysis the dualism of Virchow's school, as implied in the separation of phthisis from tuberculosis, is in a larger sense implicit also in the morphological dualism of infiltrative and nodular tuberculosis left to us by Laennec. Both camps, we must say, were equally unaware of the emergence, from their observations, of the vast problem of the twofold reaction forms. Even the subsequent discovery of the tubercle bacillus served only to increase the complexity of this problem which is still with us to-day. After two generations of pathologists and phthisiologists grappling with this problem we now have the new monistic school (Huebschman, etc.) and the new dualistic school (Aschoff, etc.). In the final analysis these represent only differing interpretations of pathogenesis of the two basic reaction forms, their relationship to and frequent transitions between one another. While, before, the problem remained largely academic and of interest chiefly to morphologists, it has become of great clinical practical significance since the recent discovery of the infiltrative incipiency of chronic pulmonary tuberculosis (Assman, Redeker, etc.).

It is now a well recognized fact that in a considerable number of cases the early infiltration marks the onset of subacute (exudative) bronchopneumonic phthisis in which the process spreads, not by dissemination of nodular lesions, but by contiguous or metastatic infiltrations. At autopsy, then, no nodular tubercle may be in sight anywhere, all is diffuse infiltration and caseation. It is also a well recognized fact that a considerable proportion of early infiltrations, particularly if treated early, resolve without giving rise to bronchogenic dissemination, hence do not go on to progressive productive phthisis.

In contrast to these two forms, in which no nodular tubercle develop in the course of phthisis, stand the bulk of cases in which transition to chronic bronchogenic ("tubercular") phthisis is the ultimate issue. Looking at the process in the state of initial infiltration, it may indeed be said with a great deal of truth that "the greatest danger for most phthisical patients is that they may become tuberculous." The implication is, then, that the acute infiltration has developed into chronic bronchogenic phthisis; an issue which we are now accustomed to watch with anxious dread in every case of early phthisis.

TUBERCULAR AND PNEUMONIC PHTHISIS IN DIFFERENT EPIDEMIOLOGICAL PHASES

In a recent presentation,[2] I discussed the changes taking place now in our midst with the shift in the epidemiology of tuberculosis. I stressed particularly the peculiarities of the early exudative reactions in young adults who now come under heavy exposure with lack of the type of permanent allergy possessed by previous generations. The potentialities of these early exudative lesions are just those three discussed above, namely:

1: Resolution without phthisical evolution.
2: Evolution in form of acute exudative (florid) phthisis.
3: Evolution of chronic bronchogenic phthisis.

It would seem to me that the cleavage between the two reaction forms, acute exudative (pneumonic) phthisis and chronic nodular (tubercular) phthisis, becomes particularly sharp when the epidemiological constellation is such as to bring about contact between long exposed (long tuberculized urban individuals) and recently slightly or not exposed (non-tuberculized rural) individuals. Possibly it was the observation of just such a material which in their time lead Virchow and his pupils to take their famous dualistic stand. In such material, the contrast between infiltrative and nodular tuberculosis is so sharp that a bridge between them is difficult to conceive.

On the relationship between infiltrative and nodular tuberculosis, Laennec had the following to say: (Laennec, R. T. H.: De l'auscultation mediate, translation by W. Hale-White, London, 1923, pp. 41–42.)

Sometimes I have observed the last mentioned (tuberculous infiltration of the lung) in lungs affected with peripneumonia, and even in the hepatized portion. The small number, limited extent and very pale colour of the tuberculous masses made it evident that they were of recent formation, but from this we must most certainly not conclude that the tubercles were the outcome of inflammation, for besides such a case being extremely rare when compared with the frequency of hepatization of the lung, I have also found the same rarity of tubercles at the same stage and patients whose lungs were in all other respects perfectly healthy. Bayle has moreover proved conclusively that tubercles cannot be regarded as a result of the termination of inflammation. It cannot be denied that peripneumonia both acute and chronic is sometimes coexistent with tubercles. It is even probable that it may occasion their de-

[2] Pulmonary tuberculosis in the present epidemiological phase, Canadian Tuberculosis Association Meeting, Toronto, June 30, 1940.

velopment in patients already predisposed; whereas in other cases the irritation set up by the presence of tubercles in appreciable numbers may determine peripneumonia. We cannot but give credence to these two possibilities in view of repeated post mortem examinations. On the other hand, a multitude of facts shows that the development of tubercles is the outcome of some general condition, that it most often takes place without any previous inflammation, and that when inflammation is coincident with tubercular disease, it is usually of later date.

What is here described is obviously the exudative pneumonic extensions common at the terminal phase of chronic productive phthisis, well recognized as such. This is of course the reverse sequence of events, namely, the transition from nodular to exudative tuberculosis. While less conspicuous, this transition is a quite frequent occurrence in chronic productive phthisis. In a material of predominantly chronic productive phthisis, observations of this transition might lead one to conceive a natural bridge between them. Perhaps it was the prevalence of chronic productive phthisis in the material of Laennec in the epidemiological phase of his time and place which lead him to his concept of the unity of tuberculosis.

THE CONTRALATERAL LUNG IN PULMONARY TUBERCULOSIS[1]

ANTHONY D. CALOMENI[2]

THE PROBLEM

The contralateral lung in pulmonary tuberculosis is, of course, the well, or less diseased lung. Its behavior has attracted the attention of all who treat this disease. Almost everyone has observed that the contralateral lung, in bilateral disease, may demonstrate retrogression of lesions along with, and occasionally in spite of, the collapsed side with its greater amount of disease.

It will be remembered that, until a few years ago, the employment of bilateral collapse therapy was regarded as hazardous or was avoided entirely. It was the common opinion that proper and sufficient physiological function of the lungs was not possible because of the mechanical interference. And, in the minds of many, even unilateral collapse has been thought to place too great a burden on the contralateral lung, especially if that lung was also diseased; inviting, first, respiratory embarrassment to the patient and, second, because of the extra burden, exciting spread of disease. Gradually these latter conceptions have been discarded through increasing clinical experience in collapse therapy (7, 9), but the fear of bilateral collapse remained for some time longer. Probably as a corollary to this distrust came the first observations on the contralateral lung from some of the earlier workers. Although large-scale studies on this particular phase, as such, were not available, isolated cases were reported occasionally in the literature (1, 2, 6, 8, 11, 12, 13). Foix (3), in 1928, reported the belief that unilateral pneumothorax had a distinctly beneficial effect on lesions of the other lung. Later, others bore out this belief in small reported series.

From time to time, in articles on collapse therapy appeared a notation, more or less parenthetical, pointing out the beneficial effect manifest in the contralateral lung (5, 7, 9). O'Brien (7) called attention to the response made by the contralateral lung in one of his studies covering a

[1] From the Wm. H. Maybury Sanatorium, Northville, Michigan.
[2] Saginaw County Hospital, Saginaw, Michigan.

series of phrenic nerve operations in 1930. He pointed out that collapse therapy rarely exerts a harmful effect on lesions in the so-called good lung; and further, that in more than 78 per cent of 288 patients with bilateral disease the lesions in the contralateral lung either healed completely or improved following phrenic operation on the more diseased side.

Matson *et al.* (5), in 1925, implied that the contralateral lung will often take care of itself when the more diseased side is brought under control, regardless of the collapse procedure employed. Whereas O'Brien's observations were on patients with phrenic operation only, a recent report from the Hudson County (New Jersey) Tuberculosis Hospital (4) mentioned the same effect on patients receiving unilateral pneumothorax.

A statistical study of the fate of the contralateral lung seems particularly pertinent at the present since in recent years the use of collapse therapy has been increased in the treatment of tuberculosis, and particularly in bilateral disease. In many hospitals and sanatoria collapse therapy is used nowadays in from 60 to 80 per cent of cases. Furthermore, the use of simultaneous bilateral collapse therapy has increased even more strikingly; until the past decade it was scarcely used at all. Since it has been found not only possible, but also profitable on occasion to collapse both lungs at the same time, it is not uncommon to find 20 per cent of an institution's patients receiving treatment to both lungs. Therefore, a useful purpose may be served by investigating the behavior of the contralateral or "good lung," since this is often an incalculable factor which may heavily influence the formulation and the outcome of any program of active surgical treatment.

CONDITIONS OF THE STUDY

In the observations to be presented the terms "collapse" and "collapse therapy" are used interchangeably and are to be understood to include phrenic nerve interruption, pneumothorax and a combination of both. A series of cases has been investigated with a view toward determining what effect unilateral collapse had on the opposite or contralateral lung in (*1*) bilateral disease, (*2*) unilateral disease in which the other lung showed healed lesions, and (*3*) unilateral disease in which the opposite lung was clear.

In addition, a second group of patients is presented on whom no collapse measures were employed. A similar classification was used for these cases, in following the fate of the contralateral or "better" lung.

The data for this paper were obtained at the William H. Maybury Sanatorium, Northville, Michigan. The cases which fulfilled the requirements for this study were taken in consecutive order, as they appeared among the 1,879 patients admitted during the three years beginning January 1, 1929 and ending December 31, 1931. No patient under sixteen years of age was considered in this group and none who remained under sanatorium care less than three months. No distinction was made between male and female, nor between colored and white patients. All cases meeting these conditions were studied from the time of admittance to the hospital. Survey of each patient was terminated under one of three conditions: discharge with maximum benefit, institution of further collapse surgery or death.

Although this study is primarily concerned with the conditions demonstrated by the contralateral lung, the effect on the collapsed side was also noted, and the data recorded side by side with that of the opposite lung for the purpose of clarity and comparison. In the second or uncollapsed group the effect on both lungs was also recorded.

Since our basic concern is the determination of the satisfactory or unsatisfactory progress of disease in both the collapsed and contralateral lungs, it was necessary to reckon progress from serial X-ray films in all cases, together with sputum findings in as many cases as possible. The following conditions were used in determining favorable or unfavorable progress.

(*1*) Exudative disease: Progressive absorption or fibrosis of exudative infiltrations was considered favorable. Lack of change was regarded as unfavorable, unless the infiltrations were originally fibrotic; in such cases an unchanging lesion was considered favorable. Extension of infiltrations was unfavorable.
(*2*) Cavities: Roentgenographic evidence of complete closure of cavities was considered favorable. Persistence of cavity, whether smaller, unchanged or larger, was unfavorable.
(*3*) Sputum: Conversion of positive to negative sputum, or persistence of negative sputum was considered favorable. Sputum must have been consistently negative on repeated examinations for at least six months. Continued positive sputum was considered evidence of unfavorable progress, provided it could be determined which side was the source.

In a lung showing both exudative disease and cavity, unfavorable progress in either one was definitive. For example, cavity closure with

increase of infiltrations, or progressive fibrosis with persistence of cavity, was recorded as unfavorable. Sputum findings obviously could not always be used as a criterion of progress in single lungs individually considered. For example, a patient's "better" lung might show favorable progress of a small infiltration, while the sputum remained positive because of an ineffective pneumothorax with open cavity in the "worse" lung. Such a case would be recorded as showing improvement in the contralateral lung, while the treated side would be recorded as unsatisfactory. Since a moderate number of cases present such a situation, the collapsed side in some of the following tables shows a lower rate of satisfactory progress. This should not, however, always imply an unsatisfactory result because further treatment (excluded from this study) was effective in many of such cases.

Since each lung was considered separately it became necessary to give to each lung a separate diagnosis. The classifications were chosen arbitrarily, and of course maintained uniformly throughout the study, as follows:

1: Infiltrative disease anywhere in the lung, no greater in extent than could occupy the upper lobe down to the second anterior rib, was classified as minimal.
2: Disease occupying up to one-half the lung without cavities, or with cavities having a total diameter less than four centimetres, was classed as moderately advanced.
3: Disease occupying more than one-half the lung, regardless of cavities, was diagnosed far advanced.

Six different classes are thus possible, considering the state of both lungs. Cases are included some of which fulfill the definitions of each class, as follows:

CLASS	CONTRALATERAL SIDE	WORSE SIDE
I	Minimal	Minimal
II	Minimal	Moderately advanced
III	Minimal	Far advanced
IV	Moderately advanced	Moderately advanced
V	Moderately advanced	Far advanced
VI	Far advanced	Far advanced

These groupings will be referred to as class I, class II, etc. in the remainder of the paper.

STATISTICAL DATA

Table 1 represents a group of cases with active bilateral disease in which only one side (the side of greater disease) received collapse therapy. In almost every one of the classes there is a slightly higher percentage of improvement seen on the contralateral side than on the collapsed side. This paradox, as explained before, simply means that the treatment employed was not sufficient to produce a satisfactory result on the most involved side and had to be augmented with further measures to bring about satisfactory control of the worse side.

We may justly infer that, even though the treatment applied is sometimes insufficient to control the disease on the side concerned, the contralateral lung, though also diseased (particularly if by infiltrative lesions), is usually aided, frequently to a remarkable degree, by collapse of the worse side.

TABLE 1

Bilateral active disease—unilateral collapse

	CONTRALATERAL SIDE UNCOLLAPSED			WORSE SIDE COLLAPSED	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	10	Min.	100	Min.	90
II	43	Min.	86.0	Mod. adv.	88.3
III	39	Min.	79.5	Far adv.	66.6
IV	45	Mod. adv.	84.4	Mod. adv.	73.3
V	68	Mod. adv.	76.6	Far adv.	76.6
VI	41	Far adv.	60.9	Far adv.	51.2
Totals.....	246		78.4		72.7

In the 246 patients studied in this group, although there is a slightly higher percentage improvement on the contralateral side (78.4 per cent as against 72.7 per cent), there is a hand-in-hand improvement of the two sides. It is also plain, as one might expect, that the more extensive the disease, whether on one or both sides, the less is the rate of improvement.

Table 2 deals with a group of patients similar to those in table 1, that is, patients with bilateral disease, with the exception that bed-rest alone was employed. As stated earlier, all conditions for these two groups except collapse therapy were equal on the average. This second group was therefore considered a suitable control of the first group. The lung

which presented the smaller amount of disease was chosen as the "contralateral lung."

In this group, as in the first, there is again shown in the totals a corresponding improvement for the two sides. There is however a remarkable difference in the total rate of improvement between the corresponding sides for the two groups: 78.4 per cent improvement of the contralateral side in group I, as against 54.6 per cent in group II; 72.7 per cent improvement of the more involved (collapsed) side in group I, as against 53.5 per cent on the more involved (but uncollapsed) side in group II. The most important difference appears in classes V and VI of the one group as compared with the same classes in the other. Remembering the parallel improvement shown by both sides in each group, the marked

TABLE 2

Bilateral active disease—no collapse

CONTRALATERAL SIDE				WORSE SIDE	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	7	Min.	100	Min.	100
II	4	Min.	100	Mod. adv.	100
III	0	Min.	0	Far adv.	0
IV	23	Mod. adv.	82.6	Mod. adv.	78.2
V	16	Mod. adv.	31.3	Far adv.	31.3
VI	38	Far adv.	34.3	Far adv.	34.3
Totals.....	88		54.6		53.5

difference in total improvement speaks for the employment of prompt and adequate collapse therapy in bilateral disease, at least on the more involved side.

Generally we can predicate from the foregoing figures that, as the disease of the more involved side progresses or retrogresses, the contralateral side does likewise. And if the more involved side, being brought under control by adequate treatment, is associated with a 78.4 per cent improvement in the contralateral lung in bilateral disease, the employment of bilateral collapse measures should not be hastily decided upon simply because bilateral disease exists. In cases with advanced disease on both sides, however, the contralateral lung is likely to benefit less from treatment of the opposite side. The figures indicate that the greater the amount of disease present, the more necessary becomes the

need for bilateral collapse, except where contraindications exist. The studied judgment required of those treating pulmonary tuberculosis becomes the more necessary when results, such as presented here, are brought to our attention.

Table 3 represents a group of patients with unilateral active disease. The contralateral lung showed a healed lesion, healing having taken place by fibrosis or calcium deposit. This group was studied to deter-

TABLE 3

Unilateral active disease—unilateral collapse

CONTRALATERAL SIDE UNCOLLAPSED—HEALED				WORSE SIDE COLLAPSED	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	2	Healed	100	Min.	50
II	10	Healed	80	Mod. adv.	70
III	14	Healed	92.8	Far adv.	64.4
Totals.....	26		88.4		65.3

TABLE 4

Unilateral active disease—no collapse

CONTRALATERAL SIDE HEALED				WORSE SIDE	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	4	Healed	100	Min.	100
II	1	Healed	0	Mod. adv.	0
III	2	Healed	50	Far adv.	0
Totals.....	7		71.4		57.1

mine what might occur to the healed lesions in the contralateral lung, as the disease on the worse side progressed or improved under treatment. In 26 patients, the contralateral healed lesions remained inactive in 88.4 per cent, while 65.3 per cent showed improvement on the collapsed side.

In table 4 patients are presented with healed lesions of the contralateral lung and active disease in the other lung. No collapse, however, was employed on the side of active disease. As might be expected, only a few cases were found to represent this group since such patients were usually given collapse therapy, even in the first year of the study. Fur-

thermore, only a few patients appear with healed lesions on one side while active disease is present on the other. Although in both groups III and IV the number of cases is comparatively small, we can see an important result in the total percentages in the two groups. First, the contralateral lung in group-III patients who had collapse therapy shows a greater protection of healed lesions (88.4 per cent) than does the corresponding lung (71.4 per cent) in similar cases of group IV when the

TABLE 5

Unilateral active disease—unilateral collapse

CONTRALATERAL SIDE UNCOLLAPSED—CLEAR				WORSE SIDE COLLAPSED	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	30	Clear	93.3	Min.	96.6
II	70	Clear	94.2	Mod. adv.	84.1
III	57	Clear	89.4	Far adv.	84.2
Totals.....	157		92.3		87.2

TABLE 6

Unilateral active disease—no collapse

CONTRALATERAL SIDE CLEAR				WORSE SIDE	
Class	Number of Cases	Diagnosis	Per cent Satisfactory	Diagnosis	Per cent Satisfactory
I	23	Clear	95.6	Min.	95.6
II	6	Clear	83.3	Mod. adv.	100
III	5	Clear	60	Far adv.	60
Totals.....	34		88.2		91.1

diseased side is uncollapsed. Second, the diseased collapsed side shows an even more favorable response, compared to the diseased uncollapsed side. When we consider the moderately and far advanced sides of the group receiving collapse, with 70 per cent and 64.4 per cent improvement, respectively, as against 0 per cent and 0 per cent improvement of the corresponding diseased lung in the group receiving no collapse, the difference becomes the more remarkable.

Table 5 presents a rather large number of patients with unilateral disease, whose contralateral lung was clear. These patients received

active treatment of the diseased side. Here, as in preceding groups, the contralateral lung was observed during the course of treatment of the diseased side. Out of a total of 157 patients, in 92.3 per cent the contralateral side remained clear, while 87.2 per cent showed improvement of the diseased side.

Table 6 presents a group of patients with unilateral disease whose contralateral lung was clear, as in group V, but in whom the diseased side received no active treatment. Of 34 cases, 88.2 per cent did not develop any lesions in the clear contralateral lung, while 91.1 per cent showed improvement of the untreated diseased side.

An observation of note is to be found here in class II and class III of tables 5 and 6. Though only a comparatively small number of cases is presented in classes II and III of table 6, there is a distinct tendency to greater spread of disease to the uninvolved side in unilateral disease that is uncollapsed, as compared with similar groups in table 5 in which the diseased side has received collapse therapy.

DISCUSSION

A fault frequently chargeable against statistical studies in the treatment of tuberculosis is the lack of an accurately comparable control series. Data obtained from records in two or more institutions, or data from one institution at different periods, are open to the criticism that the patients present wide variations in racial groups, economic status and percentage of advanced cases. Even the type of routine hospital regimen may be subject to wide variation in the nursing care, the diet and the amount of exercise permitted or required.

Such sources of statistical error have been obviated to a large extent in this study for the following reasons. The period of time involved is three consecutive years, 1929, 1930 and 1931. All the patients were treated at one institution, under identical conditions of general medical management, diet and bed-rest. All the patients were derived from a single community, which provided a number of different racial groups, but which provided them in roughly equal proportions throughout this period. The program of case-finding in the community was unchanged during this period, so that similar proportions of early and advanced cases were admitted during the three years.

But, perhaps of more importance, the selection or rejection of cases for collapse therapy was subject to a marked variation in this short time.

This change, however, is not referable to a change in the type of cases, but represents an alteration in the criteria for surgical interference and in the attitude of the patients toward collapse therapy. In 1929, active treatment was used sparingly, and not unnaturally a considerable number of patients refused collapse treatment even when offered. The year 1930 saw a broadening of the indications for phrenic paralysis and pneumothorax, so that by 1931 treatment was used much more frequently. At the same time an increasing understanding of collapse therapy on the part of patients resulted in fewer refusals of treatment. Thus the first portion of the three-year period has provided most of the cases in our "control" series who did not receive collapse treatment; and the latter portion, most of those who did.

In recent years a number of investigators have advanced several theories to explain the mode of action whereby improvement takes place on the contralateral side. Patior and Swyngedauw (8) and others (1, 2, 10, 13) believed with Rist and Mantoux that the mechanism of the contralateral effect occurs *via* the mobile mediastinum. Likewise the Italian writers are of the opinion that mobility of the mediastinum is a prerequisite for a favorable effect of contralateral pneumothorax. They believed the contralateral effect of pneumothorax is elective, that is, more effective local relaxation of pulmonary tissue is brought about (especially when lesions are limited to a single lobe) as the result of a combination of two phenomena: lesional retractility added to pulmonary elasticity. This combined action allows a diseased lobe to retract much more than the adjoining lobes in which elasticity alone is concerned.

Schill (11) stated that decreased toxaemia may be partially responsible for the beneficial effect which follows unilateral collapse. Schill further believed that the effect was due partly to an increase in intrathoracic pressure of the contralateral side. By careful quantitative measurements of the pressure in both pleural cavities in unilateral pneumothorax, he demonstrated a definite increased pressure in the contralateral pleural cavity.

Schuberth (12), reporting improvement in the contralateral lung following phrenic exeresis on the most involved side, attributes this improvement to displacement of the mediastinum into the opposite direction following operation. The immunological concept of local allergy, the "cellular factor" suggested by Foix, may also play a part. It is likely that all these mechanisms in combination are responsible for the beneficial effect.

SUMMARY

The contralateral lung was studied in 558 cases which were divided into two large groups: those receiving collapse therapy and those receiving bed-rest alone. The group receiving no collapse was employed as a control. Each group was subdivided into three divisions: (*1*) bilateral disease, (*2*) unilateral disease with contralateral lung showing healed lesions, (*3*) unilateral disease with the contralateral lung clear.

In bilateral disease, cases receiving unilateral collapse showed a much greater tendency toward improvement of the contralateral lung (78.4 per cent) than control cases (54.6 per cent) receiving no collapse.

In patients with unilateral disease (collapsed) in whom the contralateral lung showed a healed lesion, reactivation occurred in fewer patients (11.6 per cent) than in those whose diseased side was uncollapsed (28.6 per cent).

Cases with a clear contralateral lung in whom the diseased lung was collapsed showed only a 7.7 per cent spread of disease to the clear lung, as compared to 11.8 per cent spread to the clear lung in cases with uncollapsed diseased lung.

CONCLUSIONS

Unilateral collapse therapy for pulmonary tuberculosis not only promotes healing of the treated side, but also encourages to a remarkable degree, and in a large number of cases, healing in the contralateral lung when that lung is also diseased. It protects the contralateral lung from reactivation when that lung shows a healed lesion; and, finally, it protects the contralateral lung from invasion by new disease when that lung is clear.

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BRONCHIAL STENOSIS AND UNEXPANDABLE LUNGS[1]

Report of Two Cases

JASON E. FARBER

Reference (1, 2) has been made to the rôle of bronchial lesions as a factor in the production of an unexpandable lung. It was suggested that, if occlusion is present, the probable sequence is atelectasis followed by irreparable and irreversible pathological changes in the lung, making reëxpansion impossible. An ulcerative tuberculous tracheobronchitis with bronchial stenosis may lead to similar parenchymal alterations. Instances of this kind have been described (3). Stenotic but nonoccclusive tuberculous bronchial lesions may contribute by producing a nonspecific pneumonitis followed by extensive intrapulmonary fibrosis. The following case reports are of interest in this connection.

CASE REPORTS

1: No. 354521. A. M., white female, age twenty-nine, relates a history of bronchial asthma since 1931, with wheezing, cough and expectoration. Pulmonary tuberculosis was diagnosed in August, 1932 when a positive sputum was found. Therapeutic pneumothorax of the left lung was initiated in October, 1932. In spite of pneumothorax a productive cough has persisted. The sputum has been mucopurulent or purulent in character. Dyspnoea on slight exertion has been present. Periodically, since the onset of the illness, the patient has suffered from "colds," as she describes them, with malaise, fever, pain in the chest and anorexia. Expectoration is generally increased at this time and is usually purulent. At other times there is a sudden cessation of expectoration lasting for about a day and accompanied by general discomfort and fever. The patient usually feels ill at the time but is relieved when expectoration returns. These peculiar and characteristic illnesses have gone on for years, increasing in frequency and severity of late. The sputum has been negative for several years. During 1939 and 1940 attempts were made to reëxpand the collapsed lung, but without success. Refills were abandoned for several months and no appreciable reëxpansion occurred. Roentgenograms (figures 1, 2 and 3) of the chest show the collapsed lung. Fluoroscopy disclosed an immobile lung and mediastinum.

[1] From the Tuberculosis Service of the Edward J. Meyer Memorial Hospital and the University of Buffalo Medical School, Buffalo, New York.

On June 25, 1940 bronchoscopy (Doctor Gerstner) showed a considerable amount of pus in the trachea. The carina appeared to be displaced to the left. The left main bronchus was closed off just after its beginning by a mass of scar tissue with a pin-point opening (figure 4). Creamy pus could be seen oozing through this opening. The pin-point opening was dilated with a number 9 French bougie. The lumen appeared larger after dilatation. On September 10, 1940 bronchoscopy revealed a similar picture except that the opening in the dense mass of scar tissue obstructing the bronchus was the size of a match head. Again pus could be seen trickling through the bronchial orifice. This time the bronchus was dilated with a number 10 French bougie. On October 22, 1940 bronchoscopy (Doctor Bozer) showed "the orifice of the left main bronchus to consist of an opening approximately 2 mm. in diameter. This had inflammatory edges and thick white non-foul pus oozed out from below."

2: No. 426950. M. M., white female, age thirty, clerk, has experienced since May, 1932 asthma-like wheezing, dyspnoea on exertion and often at rest, and a sensation of heaviness in the chest. Since that time a productive cough has also been present. In September, 1932 the sputum was found to contain tubercle bacilli. A roentgenogram of the chest showed a moderately advanced tuberculosis of the left lung. Therapeutic pneumothorax was induced in January, 1933. Soon thereafter, a small effusion appeared in the pleural space. It was aspirated and there has been no recurrence. In September, 1933 a pneumonolysis was performed. Since then the sputum, although mucopurulent in character, has been reported negative. However, a gastric lavage in September, 1939 showed tubercle bacilli. The pneumothorax has been maintained and, of late, refills of small amounts (100 cc.) of air have been given once a month. Since the onset of her illness the patient has had intervals in which there has been a copious bronchorrhoea, often lasting for several days.

FIG. 1 (upper left). Case 1. An unexpandable lung on the left, four years after pneumothorax was induced. The mediastinum is displaced to the left. Pulmonary markings cannot be visualized.

FIG. 2 (upper right). Case 1. The same patient four years later. There is no essential change in the appearance of the collapsed lung.

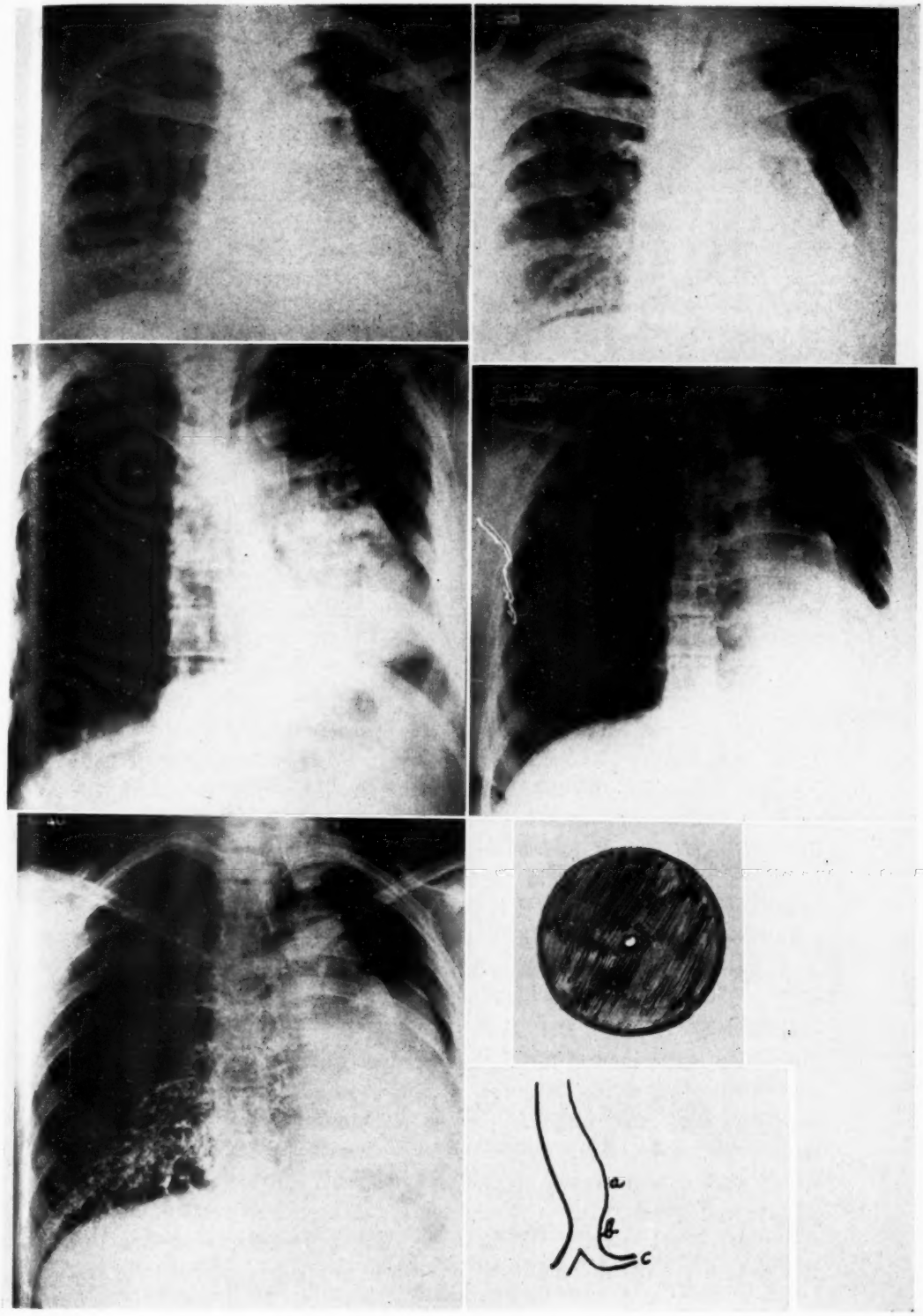
FIG. 3 (center left). Case 1. The same as in figure 2 with Bucky-Potter diaphragm technique, showing honeycombing throughout the collapsed lung.

FIG. 4 (right bottom, upper). Case 1. Bronchoscopic view of the stenosis of the left main bronchus. There is almost complete occlusion.

FIG. 5 (center right). Case 2. An unexpandable lung on the left, eight years after onset of pneumothorax. The trachea and mediastinum are displaced to the left.

FIG. 6 (lower left). Case 2. Bronchogram of the same patient which shows narrowing of left main bronchus. Lipiodol did not enter the collapsed lung.

FIG. 7 (right bottom, lower). Case 2. Diagram of bronchial tree as seen on lipiodol film. Note trachea appears dilated at *a*, and narrowed at *b*. At *c* the left main bronchus appears stenotic.



FIGS. 1–7

At times there is a sensation of "rattling or knocking" in the left side of the chest. The patient notes that when lying in bed a change in position affects both the cough and rattling. During these years the patient has had numerous "colds" accompanied by an increase in cough and expectoration. The sputum at the time is usually purulent. On physical examination the patient appeared in good health. Rhonchi were felt and heard over the left chest. The physical signs of pneumothorax were otherwise present. Fluoroscopy showed a fixed collapsed left lung and an immobile mediastinum. This was confirmed by roentgenography (figure 5) of the chest.

On bronchoscopy there was noted an eccentric scarring of the trachea just above the carina. The carina and the left main bronchus could not be visualized but the right main bronchus was seen. The stenosis of the left bronchus allowed the passage of a number 14 French bougie.

Bronchograms (figure 6) with lipiodol showed a narrowing of the trachea immediately above the bifurcation. The trachea appeared considerably displaced to the left. There seemed to be almost complete obstruction of the left main bronchus about 2 cm. distal to the tracheal bifurcation (figure 7).

Refills were abandoned for approximately two months in an attempt to reëxpand the lung. No definite reëxpansion occurred. Instead, fluid began to accumulate in the pleural space.

DISCUSSION

In the two patients described the collapsed lungs are unexpandable. In neither instance was there a significant pleuritis or fluid of long standing that could cause a pachypleuritis, thereby interfering with reëxpansion. In both cases there appears to be extensive intrapulmonary fibrosis. Certainly there was originally disease of moderate anatomical extent that could account for some of the fibrotic tissue. However, the question arises whether the wide-spread parenchymal scarring can be solely explained by the healing of the tuberculous process under collapse. A stenotic obstructive bronchial lesion was also present for years in both patients. Clinically, both patients experienced episodes of pneumonitis described as "colds." At such times the catarrhal symptoms were intensified with increased cough and expectoration of mucopurulent and purulent sputum. At other times, in one instance (case 1), the expectoration would stop abruptly and the patient would experience malaise and fever. Such episodes were frequently followed by increased cough and expectoration of frankly purulent sputum. The clinical picture in these patients conforms to that of bronchial obstruction and suppurative pneumonitis. It is known that repeated performances of this nature are usually followed by structural changes in the lung and

that fibrosis and suppuration are generally present. Bronchial involvement plays a vital rôle in chronic inflammatory changes in the interstitial tissue. Pinner (4) noted that the anatomical bronchial alterations resulting from scarring following an ulcerative inflammatory process serve as an important factor in the self-perpetuating nature of the pneumonitis, chiefly by favoring retention of inflammatory products. As Pinner states it, "the fibrosing and stenosing process leads to stasis and stagnation of secretions and septic products in the lung thus promoting the intrapulmonary inflammatory state that ends in scarring, altered architectural pattern and functional disability. Organization takes place in the intraälveolar and in the interstitial exudate. Its eventual result is fibrosis and secondary emphysema. Often the fibrosis is particularly massive in the interlobular septa and peribronchially. Within large fibrotic areas small residual abscesses are frequent." These significant histological pulmonary changes serve as a basis for our understanding whereby a therapeutically collapsed lung complicated by bronchial stenosis may fail to reëxpand. These changes further suggest that vigorous attempts to reëxpand such lungs are probably inadvisable, generally ineffective and sometimes dangerous. Consider the not infrequent occurrence of empyema when attempting to reëxpand these shrunken, sclerotic masses of collapsed lung tissue.

The two cases here reported demonstrate that the bronchial lesion is a definite factor in the pathogenesis of unexpandable lungs. It seems worthy of mention that, in a previous series of cases (2) of unexpandable lungs, three of the patients had bronchial lesions, two of which were bronchoscopically demonstrated. In one of these there was a marked stenosis which after several bronchoscopies was found to have become a complete bronchial occlusion. Finally, reference is again made to the cases of Barnwell (3). Two of his patients had collapsed lungs which failed to reëxpand. There was clinical and bronchoscopic evidence of tuberculous bronchitis and stenosis. At autopsy, one of the patients was found to have an extreme bronchial stenosis and the associated collapsed lung was a small, shrunken, fibrotic mass, solid in consistency and showing ulcerated dilated bronchi throughout. This is the picture of massive parenchymal fibrosis, bronchiectasis and pneumonitis.

SUMMARY

Two patients with unexpandable lungs and stenotic bronchial lesions have been described. In both cases the dominating clinical picture has been that of pulmonary suppuration and pneumonitis in addition to an

asthma-like syndrome with wheezing and dyspnoea. Attempts at re-expansion of the collapsed lungs were unsuccessful. The visceral pleurae have not been unduly thickened by pleurisy or effusions thus preventing reëxpansion. Extensive intrapulmonary fibrosis is considered to be the important factor preventing reëxpansion in these cases. There is sufficient evidence to suggest that a distinct and a significant part of this massive parenchymal scarring followed a nonspecific pneumonitis. The latter, in turn, was caused by a nonocclusive tuberculous bronchial stenosis.

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THE PARAFFIN PACK IN THE TREATMENT OF PULMONARY TUBERCULOSIS[1]

FELIX OTTAVIANO

In a recent communication our first series of 25 cases of apicolysis with paraffin plombage were reviewed. It is the purpose of this paper to present a subsequent series of 20 cases with a four-year survey of the entire group.

The original grouping as to indications (ideal, favorable and unfavorable) is still maintained, although the first two are now considered as one. The reason for this is that the results show the particular type of lesion or lesions included in the first two groups to be amenable to this treatment. The first group will be known now as the favorable and will consist of unilateral lesions, with or without cavitation (not too large), which do not extend below the sixth posterior rib; or of bilateral lesions where the contralateral disease is not extensive or is at least definitely inactive.

It is interesting to note that of the first 25 cases, of which 11 were of the favorable type, only one of this latter group has returned to the sanatorium for removal of the pack. This has been done; the paraffin has been replaced with a fatty graft and his sputum is still negative. Of the remaining 14 who were in the second or the unfavorable group (for the most part old, unsuccessful thoracoplasties), 6 have left the institution as apparently arrested, and at their last dispensary check-up had a negative sputum and stationary lesions according to X-ray series. Of the remaining 8, 4 have had their packs removed, one is dead, 3 still have the packs but their sputum has not been converted.

The 5 cases (4 in group III and one in group II) whose paraffin has been wholly removed and one in group III which was partially removed are interesting and their histories are presented for this reason.

Case 6263: This patient had a two-stage thoracoplasty in January and February, 1936, but her sputum continued positive. She was packed with paraffin on November 11, 1936 and on December 17, 1936 her sputum became con-

[1] From Iola Sanatorium, Rochester, New York.

verted. It is still negative in spite of the fact that the pack was removed because of a bronchopleural fistula. She is now in the sanatorium but was out from September 3, 1938 to February 19, 1940. She is doing well and there has been no sign of reactivation of the disease.

Case 4324 had, previous to her pack, artificial pneumothorax in October, 1932, a phrenic nerve operation on March 10, 1932, upper stage thoracoplasty on February 27, 1936 and April 7, 1936, and, because the sputum remained positive, she was packed on July 27, 1936. Her sputum examination was negative on November 9, 1936, even though the pack was removed on October 6, 1936 because of a bronchocutaneous fistula. She had a fat transplant after the removal and left the institution on August 18, 1938. Her last dispensary follow-up shows her sputum negative on January 5, 1940, although she still has a sinus with secretions containing tubercle bacilli.

Case 7697 had pneumothorax in 1935 and a temporary phrenic in 1936; a two-stage thoracoplasty followed by anterior and posterior packs in 1936. Because of a postoperative chest hernia the pack was removed on July 22, 1938. He is still in the sanatorium with positive sputum.

Case 5256 had pneumothorax and a two-stage thoracoplasty and was packed on December 4, 1936. After working for two years, the pack was removed because of a chest hernia. A pleurocutaneous sinus remained. He is still in the sanatorium with positive sputum.

Case 8381 was packed on August 17, 1936. He was discharged on March 6, 1937 but returned on December 2, 1938 with an infected pack and a bronchocutaneous fistula. The pack was removed and replaced with a fat transplant on February 14, 1938. At this writing he is still in the institution with variable sputum, although the last test was negative. This was the only one of the favorable group.

Case 5121 had a paraffin pack on October 13, 1936 which was partially removed two years later. She had a thoracoplasty to close the cavity left by the pack removal, but the sputum remained negative. She is now working in the institution part-time.

Thus it can be readily seen that, even though these patients were in the unfavorable group, and despite the fact that the pack had to be removed, 4 of them are still negative and have left or will leave the institution.

The summary of the *unfavorable* group, then, is: 14 cases packed; 6 have left the institution as apparently arrested; one left the institution

against advice but is working; 5 are still in the institution (2 of these have negative sputum); 2 died, both from causes not attributable to the pack—making a total of 9 cases converted, 3 still positive and 2 dead.

In the second series 20 patients are presented. It will be noted that the favorable group here predominates. The number of cases now presented is not so large as was the number in the first series which covered a greater period of time. This is obviously due to the drop in the thoracoplasty group. Many of these patients would have had thoracoplasties if plombage were not a procedure at this institution. Several of them would have been poor surgical risks for thoracoplasty and would have had to lie in bed hoping that bed-rest alone would convert their sputum. A brief summary of their individual dispensary follow-ups will probably show the results better than any discussion.

Case 3936 was packed on April 3, 1937 and discharged on November 3, 1937. The out-patient clinic classification of May 13, 1940 is "inactive and satisfactory, sputum negative."

Case 9122 was packed on May 28, 1937 and discharged on October 18, 1937. The clinic note of April 16, 1940 was "inactive and satisfactory, sputum negative."

Case 9243 was packed on September 28, 1937 and discharged on May 17, 1938. The clinic note of January 5, 1940 was "inactive and satisfactory, sputum negative."

Case 9330 was packed on January 8, 1938 and discharged on May 20, 1939. Sputum was negative on May 11, 1939. The last clinic report on May 27, 1940 was "active but satisfactory, continuing cure at home."

Case 8960 was packed on January 28, 1938. Sputum was negative on October 15, 1938. He was discharged on December 20, 1938. Clinic note on January 2, 1940 was "active but satisfactory."

Case 8757 was packed on May 6, 1938. He was discharged on October 11, 1938. Last follow-up on June 17, 1940 was "inactive, satisfactory, sputum negative."

Case 8989 was packed on June 17, 1938 and discharged on January 17, 1939 as apparently arrested. Last clinic follow-up was "inactive, satisfactory, sputum negative," on May 23, 1940.

Case 9553 was packed on June 24, 1938 and discharged on January 3, 1939. Last clinic follow-up was "inactive, satisfactory, no sputum," on May 21, 1940.

Case 9547 was packed on August 26, 1938 and discharged on December 26, 1939. Last clinic follow-up on December 21, 1939 was "inactive, satisfactory, sputum negative."

Case 7544 was packed on September 9, 1938 and discharged on February 18, 1939. Last clinic follow-up on November 28, 1939 was "active, satisfactory, sputum negative."

Case 9584 was packed on Sepetmber 16, 1938 and discharged on April 27, 1939. Last clinic follow-up on May 27, 1940 was "inactive, satisfactory, sputum negative."

Case 9594 was packed on November 15, 1938 and discharged on April 18, 1939 as apparently arrested, active. Last clinic follow-up on May 31, 1940 was "inactive."

Case 9220 was packed on August 27, 1937. He is still in the sanatorium. His last sputum examination was negative on August 12, 1940; he has had eleven negative examinations since the last positive on February 24, 1940.

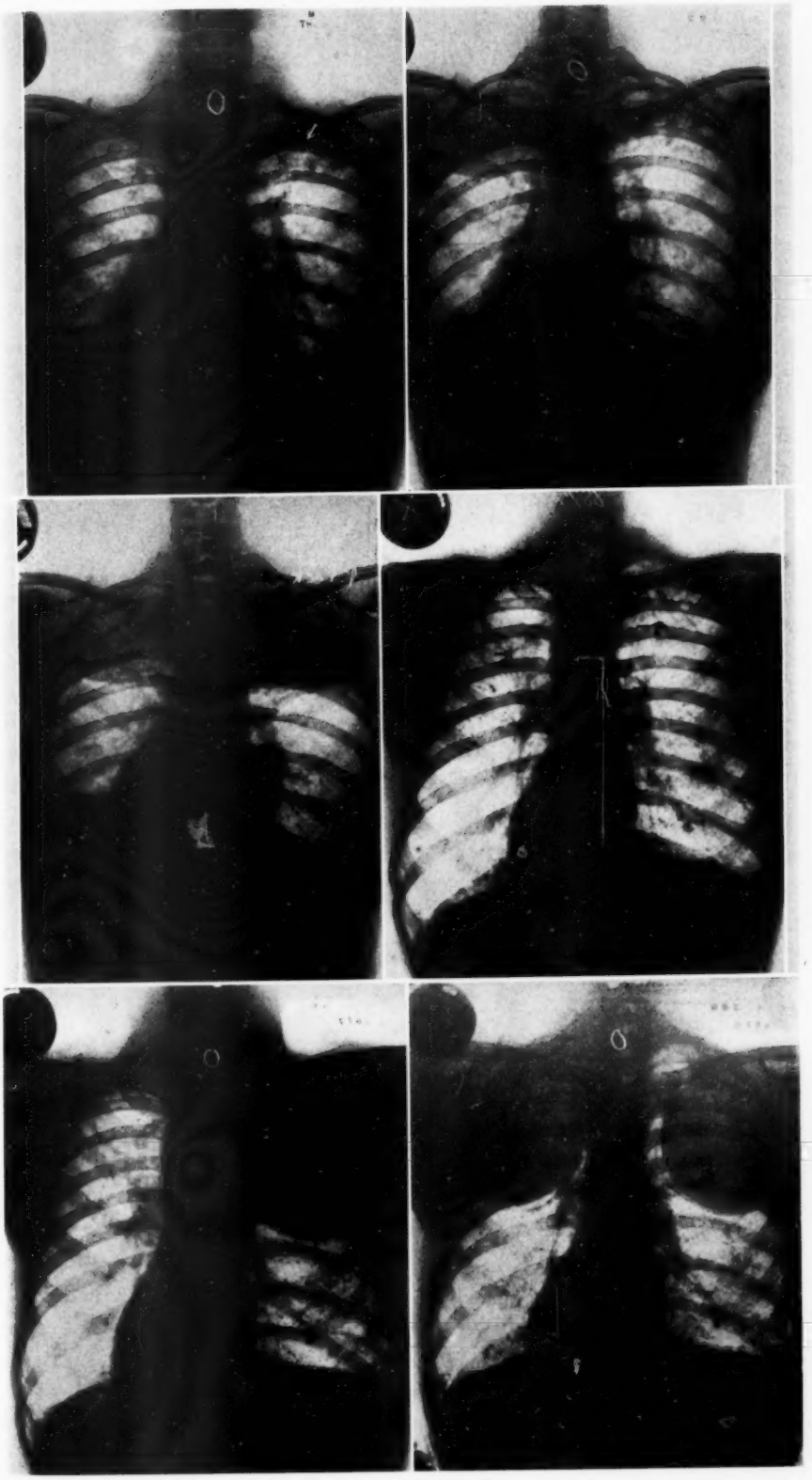
Case 8735 was packed on January 6, 1939 and discharged on October 15, 1939. Last clinic follow-up on March 5, 1940 was "inactive, satisfactory, sputum negative."

Case 9765 was packed on April 28, 1939 and discharged on March 13, 1940. Last clinic follow-up on May 6, 1940 was "active, satisfactory, sputum negative."

Case 8761 was packed on September 24, 1937 and died on September 27, 1937.

Case 9291 was packed on August 31, 1937 and died on August 3, 1938.

FIG. 1. Upper left. Case 3965. Before the first pack
FIG. 2. Upper right. Case 3965. After the first pack
FIG. 3. Center left. Case 3965. After the second pack
FIG. 4. Center right. Case 8577. Before the first pack
FIG. 5. Lower left. Case 8577. After the first pack
FIG. 6. Lower right. Case 8577. After the second pack



FIGS. 1–6

Case 8076 was packed on May 15, 1938 for haemoptysis. He was discharged on July 13, 1938 as quiescent. Last clinic follow-up was on April 24, 1940, "inactive, satisfactory;" patient is now working full-time on the staff.

Case 8871 was packed on December 1, 1939 and is still in the sanatorium. Last sputum examination on August 12, 1940 was negative.

Case 8334 was packed on January 21, 1938 and discharged on February 4, 1939; is now curing at home. Last clinic follow-up on March 11, 1940 was "active and satisfactory;" last sputum negative on March 11, 1940.

This completes the series of 45 cases, but there were 49 operations. The discrepancy is explained by the fact that 2 of the cases had anterior packs also, and 2 others had bilateral packs. Emphasis is placed on this latter category because of the unusual success obtained with two entirely different types of cases.

The first one (figure 1) is case 3965. She is the patient mentioned in the original series as the first to have received paraffin pack at Iola Sanatorium. She was discharged on August 4, 1936. Her sputum was negative. It had been planned that she was to receive a bilateral pack, but she left because of sputum conversion. Her sputum later became positive, however, so she returned and was packed on the contralateral side on January 2, 1939. Her follow-up note of March 1, 1940 was "active but satisfactory, sputum negative."

The other case, 8577, had been in the institution since December 26, 1935 and had artificial pneumothorax on the right which was discontinued. He had large, bilateral apical cavities. He was packed first on the right on June 12, 1936 and then on the left on July 13, 1937. He left the institution on October 13, 1938 as apparently arrested. His last clinic follow-up on February 2, 1940 was "inactive, satisfactory, sputum negative."

The results in both these cases need no further comment; suffice it to say there was no other hope and both have been out of the institution for some time.

Finally, the fatal cases warrant some comment because of the peculiar fact that, of the 6 dead, only 2 died from reasons even remotely related to the procedure: one (case 8761) from a massive hydrothorax, and the other (case 7182) from pulmonary emboli, both at some time after the operation. Of the other 4, one (case 7674) died on returning to the

institution (after one year) because of a reactivation of his disease following influenza. Case 9291, who was packed purely as a last measure to stop an incessant haemorrhage, lived for one year after the operation without streaking, but died from a natural and inevitable progression of his disease. Case 8620 died at home one year after his pack from causes unknown. Case 2721, who had previously had a thoracoplasty, (the only death in this group) was packed to stop continual bleeding, and here the pack had no more effect than the thoracoplasty. He died two years after the pack from a severe haemoptysis.

SUMMARY

A total of 49 operations were performed on 45 patients. The extra 4 operations are accounted for by 2 bilateral and 2 anterior packs. Five packs were removed wholly and one partially. Thirteen of these patients had previous thoracoplasty. Of the 32 without previous thoracoplasties, 23 have left the institution, 4 are still in the hospital and 5 have died. Of the 13 who had previous thoracoplasties of various stages, some two and some three, one died, 6 have been discharged with negative sputum, 2 have been discharged with positive sputum but quiescent disease, and 4 are still in the hospital. All of the 6 with negative sputum are either working or are able to work. The 2 with positive sputum are curing at home. The 4 remaining in the institution are not completely hopeless cases, for 2 have negative sputum and are trying to heal up pleurocutaneous sinuses, and the others are hoping that bed-rest or subsequent surgery will allow them to leave. In the entire series of 45 cases, 4 people coughed up paraffin, 2 are discharged and working, and 2 are still in the institution.

SUMMARY OF CASES

A. New Series		
1. Total number of cases	20	
2. Total number discharged	16	16
a. Apparently arrested	14	
b. Quiescent	2	
(1) Negative sputum	1	
(2) Positive sputum	1	
3. Still in sanatorium	2	2
a. Negative sputum	2	
b. Positive sputum	0	
4. Number dead	2	2
		20

B. All Three Groups		
1. Total number of cases	45	
2. Total number discharged	31	31
a. Apparently arrested	27	
b. Quiescent	4	
(1) Negative sputum	3	
(2) Positive sputum	1	
3. Still in sanatorium	8	8
a. Negative sputum	4	
b. Positive sputum	4	
4. Number dead	6	6
		45
C. Survey of Primary Packs		
1. Total number of cases	32	
2. Number discharged	23	23
a. Apparently arrested	20	
b. Quiescent	3	
(1) Negative sputum	3	
(2) Positive sputum	0	
3. Still in sanatorium	4	4
a. Negative sputum	2	
b. Positive sputum	2	
4. Number dead*	5	5
		32

* Only two of these directly attributable to pack.

CONCLUSIONS

There is no doubt at Iola about the part that paraffin plombage plays in the treatment of tuberculosis. When a case is in the favorable group there is no hesitation in prescribing this form of treatment. The difficulties thus far encountered are perforation (this has happened only in cases which had previous thoracoplasties, except in one instance), the subsequent spitting of paraffin and the formation of sinuses after removal. As for the operation itself it is fairly simple and offers no obstacle. There is no doubt that a much more suitable paraffin would greatly enhance the efficacy of this treatment. The melting point of the paraffin now being used is 68° to 72°C.

It is not felt here that the few unfortunate cases who have had their paraffin removed are necessarily indications of the failure of the treatment to accomplish its purpose. In the first place, even these cases have had conversion of sputum. Furthermore, many of the other forms of treatment have had higher percentages of failures (empyemas following pneumothorax and shifts and distortions following thoracoplasties) but this has not caused their dismissal as aids.

With the gaining of experience and a more careful selection of cases, it is quite certain that paraffin plombage will accomplish its purpose without the difficulties which have been mentioned in this review.

INSATIABLE PNEUMOTHORAX

Remarks to the Paper of Dr. E. Korol[1]

M. LUCACER[2]

In 1930, Burnand called attention to a phenomenon, termed by him insatiable pneumothorax, which he observed in a few cases in which he attempted to induce pneumothorax. In these cases the pleural cavity had been entered by the needle according to manometric readings and a high negative pressure was observed before, during and after air injection. Successive refills were given without difficulty in the usual amounts and intervals. Surprisingly, no adequate degree of collapse could be demonstrated roentgenologically. Only a marginal pneumothorax pocket was present, smaller than expected and unstable, disappearing within a few days, sometimes even within a single day.

Burnand, of course, warned against obvious causes of error, such as injections of air into the lung parenchyma instead of into the pleural cavity, some types of pleuropulmonary perforations, pneumothorax pockets invisible in the usual postero-anterior diameter. In fact, even rarer causes of error were reported in the literature, such as air injection into a cavity communicating with a bronchus or into the peritoneal cavity.

Burnand set forth the following facts capable of explaining, in his estimation, the occurrence of insatiable pneumothorax. His cases showed only minimal, limited, circumscribed pulmonary lesions. The lung had conserved its radiological translucency and probably its functional integrity and, as he believed, was probably "near the physiological state." Both pleural layers conserve in these cases their normal capillary vascularization so that their absorption capacity is active and efficient. That is why they "drink" the injected air. However, Burnand alleges that in the majority of these cases, after a varying but considerable number of refills, a definite and sufficient collapse is obtained because the permeability of the pleural layers eventually is impaired due to the continuous irritation by the injected air. He cites a case of Jaquerod

[1] Am. Rev. Tuberc., 1941, *43*, 190.

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who erroneously induced a pneumothorax in a patient with a normal lung and pleura and observed the phenomenon of insatiability.

In 1929, a year before Burnand's communication, Prof. M. Ascoli and I started studying contralateral primary pneumothorax (1). We tried a pneumothorax on the healthy side if pneumothorax could not be carried out on the diseased side because of pleural obliteration. In these cases we often met with difficulties when we tried to establish a lasting collapse. At that time we spoke of "drinking" pleura. After the publication of Burnand's paper we studied carefully the phenomenon mentioned. We came to the conclusion that insatiable pneumothorax occurs mainly in cases with minimal or no lesions at all and in a few cases with somewhat larger but circumscribed lesions. It is true that the absorption of air by normal pleurae is very active, but it is by no means as rapid as in cases of insatiable pneumothorax.

Starting with recent anatomical and physiological investigations (2) this writer formulated the following working hypothesis. Beside the above mentioned anatomical normality, another condition may further markedly increase the absorption capacity of the pleura and lead to the phenomenon of insatiable pneumothorax. This is a status of vagal hypertonia, constricting the bronchi and dilating the alveoli (Viola (3), Weber (4), Pari (5), Carlson and Luckhardt (6)). The constricted bronchi obstruct the outflow of the intrapulmonary air, while the dilated alveoli prevent the lung from collapsing. This condition of vagal hypertonia at the same time, by causing vasodilatation, further increases the absorption of air.

Boldacci's (7) experiments confirm this hypothesis. He discovered that in vagotonic dogs the absorption rate of air is increased and that after atropine the rate of absorption slows down.

In man, the condition of pulmonary vagal hypertonia may be part of a general vagal hypertonia, as this writer was able to demonstrate in a number of his cases, or it may be a condition restricted to the lung. This writer proposed, therefore, to use injections of atropine in cases with insatiable pneumothorax. The results have been successful (Bruno, Anzalone, Pastor and Bence, Basunti and Lenci, cited by Korol, and other authors of my knowledge). As an illustration I should like to mention 2 of my cases from an earlier paper of mine (2).

1: Case 8. P. C., male, fourteen. During the last six months the patient presented slight temperature, dry cough, loss of weight. He was admitted March 14, 1930 with the diagnosis of mainly productive infiltration of the

right upper lobe. He was in good general condition. He had normal temperature and scanty expectoration, positive for tubercle bacilli.

On May 5, 1930 a right pneumothorax was attempted, the initial readings being −18, −8; final readings −8, −5 after injection of 200 cc. of air. Successive refills were given at two, three, five and then six and seven day intervals. Initial readings were always highly negative and the final readings always approximately atmospheric. For five months, till October 2, 23 refills were given. Roentgenologically no distinct pneumothorax pocket could be seen, although the treated lung became hyperdiaphanous; or a marginal yet unstable pneumothorax pocket was visualized which disappeared within a single day. From October 2 to 9 a daily injection of 0.5 mg. of atropine (Bellafoline Sandoz) was administered, however without results. On October 10, after a refill of 500 cc. (initial readings −10, −6; final readings −6, −1), no definite pneumothorax was demonstrated on fluoroscopy. From October 10 to 17 six more injections of atropine were given. On October 17, before further refills, no collapse could be shown but, after another refill of 500 cc. of nitrogen (initial readings −10, −8; final readings −6, −1), an excellent collapse was seen. When the collapse seemed to diminish after two months another four injections of atropine brought about a definite collapse.

2: Case 5. P. P., male, twenty-six years. For two months patient ran a slight temperature. He coughed and expectorated, lost his appetite and his weight and had a small haemoptysis. He was admitted June 2, 1930 with the diagnosis of recent exudative infiltration in the left upper lobe and a few infiltrative nodes in the right apex. He was in good general condition. His temperature was about 100°F. He had scanty expectoration, positive for tubercle bacilli. His sedimentation rate was 44. On June 5 a left pneumothorax was attempted with initial readings of −20, −18, and final readings of −12, −10, after injection of 200 cc. of air. Two days later, 400 cc. of nitrogen were given with initial readings of −20, −18, and final readings of −12, −8. Successive refills were given at intervals of two, three, four, five and later six and seven days, initial readings being always highly negative, final readings approximately atmospheric. Until October 30, four and one-half months later, 22 refills had been given but no stable collapse had been obtained. On the day of, before and after a refill of 600 cc. of nitrogen (initial readings −12, −8; final readings −4, −1), no pneumothorax pocket could be demonstrated while the lung appeared hyperdiaphanous. Thereafter, for six consecutive days, we injected 0.5 mg. of atropine a day. This time, after a refill of 600 cc. of nitrogen, a good collapse was seen and could be maintained. The initial readings became less and less negative, as did the final readings. Also in this case about two months later, when the collapse seemed to diminish, another four injections of atropine brought about a definite collapse.

It is worth while to remember that, at that time, air was only used for the induction of the pneumothorax while consecutive refills were made with nitrogen. The absorption rate of nitrogen is known to be slightly less than that of air.

To summarize, so called insatiable pneumothorax occurs mainly in cases with minimal or no lesions, or with well circumscribed lesions approaching the physiological state in which the healthy pleura has conserved a normal absorptive capacity. A vagal hypertonia further favors air absorption by causing vasodilatation. In these cases the high negative readings and the fact that the refills are performed easily in normal ratios of quantity and intervals, indicate that the air injections are definitely intrapleural. However, stable pneumothorax pockets can be demonstrated roentgenologically only after a considerable number of refills. This condition can usually be corrected by administration of atropine.

It is worth while mentioning that this phenomenon often occurred in the experience of Dumarest (8) who dedicated to it an entire chapter in the latest (fourth) edition of his classic book on collapse therapy.

In a recent paper, Korol deals with the question of insatiable pneumothorax on the basis of his records "of two patients who were considered cases of insatiable pneumothorax." The patients "were given air inflations over a period of months without X-ray signs of pneumothorax." "The manometric signs," Korol states, "were usually unsatisfactory, suggesting that the needle was in the lung tissue." "At other times," he continues, "the pressure was not altered by as much as 500 cc. of air." In his second case of "tuberculosis of the right lung of six years duration in which the upper and lower lobes had undergone much fibrosis and excavation while the middle lobe became emphysematous" he claims that air was given into emphysematous vesicles and not into the pleural cavity.

It is obvious that Korol dealt with cases quite different from those described as cases of insatiable pneumothorax. Therefore, even over a period of months, he did not obtain a pneumothorax because injections were given into the lung tissue and not into the pleural cavity. Korol believes that "in the cases of insatiable pneumothorax described in the literature, futile air injections were made not into the pleural cavity, but into emphysematous bullae which existed in all cases."

"Burnand," Korol states, "observed that in these cases emphysema was present," and "most of the writers emphasized the association of this

condition with emphysema." This writer was unable to find such emphasis in the cited literature which he reviewed carefully. He found in fact only two mentionings or rather allusions to emphysema.

The first one is made by Burnand (9). While emphasizing the characteristics of the lesions in cases with insatiable pneumothorax as minimal, well circumscribed and "near the physiological state," he charges Cardis with the opinion that "sometimes it is the case of slightly emphysematous lungs." It is impossible to state, on the other hand, whether Cardis had really dealt with cases of insatiable pneumothorax as no paper has been written by him on this subject.

The second allusion is by Banaudi (10). He states that relatively recent infiltrations are rather well circumscribed and surrounded to a certain extent by normal parenchyma and that it is not rare to find an emphysematous zone around them.

As a matter of fact in none of the diagnoses of Banaudi's 9 cases, which he reports carefully and minutely, can any mention of emphysema be found.

In this writer's cases Korol may have confused emphysema with the peculiar aspect of the treated lung in these cases which appeared hyperdiaphanous, because of the air diffused in the pleural cavity, without giving an adequate and stable pneumothorax. Also Burnand and other authors spoke of the increased radiological translucency of the treated lung in their cases. This can readily be confused with emphysema.

The difficulties of pneumothorax induction in cases with marked emphysema are well known but have nothing to do with the above mentioned cases of insatiable pneumothorax. We have emphasized the fact that a high initial and final pressure is conclusive evidence of air having been injected into the pleural cavity. Korol calls this "overconfidence in the manometer as a guide to the pleural cavity," but he does not indicate any more reliable guide than manometric readings of wide amplitude.

Korol is right in affirming that "there is no known physiological or pathological state that will permit the instantaneous absorption of large quantities of air from the pleural cavities." However, an increased and abnormally rapid, though not instantaneous, absorption took place in our cases and could be corrected by atropine injections.

Korol agrees with this writer on the usefulness of atropine. In fact, he states that "it can be understood why in some cases a good pneumothorax may eventually be established after the liberal use of atropine and other bronchodilators."

Judging from his paper, Korol had no opportunity of studying true cases of insatiable pneumothorax which, after all, are rather rare. His conclusions, therefore, cannot be applied to this peculiar phenomenon.

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PATCH AND PPD TESTS AND X-RAY CORRELATION[1]

PAUL D. CRIMM, H. N. COOKSON AND M. BROADBENT

Fifteen hundred and fifty-six high school freshmen, 777 males and 779 females, of native stock, the majority ranging in age between thirteen and sixteen years, were tested simultaneously with the Vollmer patch test (Lederle) and PPD. Reactors and nonreactors alike were X-rayed.

METHOD

A solution of PPD (0.001 mg. per dose) was prepared twelve hours prior to administration; this dosage is one-fifth of the regular second strength of PPD (0.005 mg. per dose). Each individual was given this amount intracutaneously in the left arm, after the arm had been cleansed with alcohol. The right arm was cleansed and defatted with acetone and the patch test applied. The patch was removed in forty-eight hours and reaction noted. The results, however, were not considered significant until a second reading was made at the end of seven days. For example, 128 of the patch tests were positive at forty-eight hours, while 247 were positive at the end of seven days. The Mantoux test was read in forty-eight hours and again in seven days. The criterion for reading the intracutaneous test as positive was an area of erythema elevated by induration. The criterion for reading the patch test as positive was the presence of follicles on an erythematous, indurated base. In mild reactions either test on the patch may give a positive reaction.

RESULTS

The incidence of contact cases was 10.7 per cent. Four hundred and sixty-six, or 29.9 per cent of the 1,556 tested, had primary tuberculosis as evidenced by X-ray, the tuberculin tests, or both. Secondary tuberculosis, active, was not discovered in any individual, but 7 cases (0.015 per cent) had evidence of fibrosis, which was either interlobar or parenchymal. Five of the 7 individuals had primary calcification in addition to the fibrosis.

Of the total tested, 247 (15.8 per cent) were positive to the patch test, while 254 (16.3 per cent) were positive to PPD, 0.001 mg. The PPD test found 2.7 per cent more positives than the patch test. Pearse, Fried

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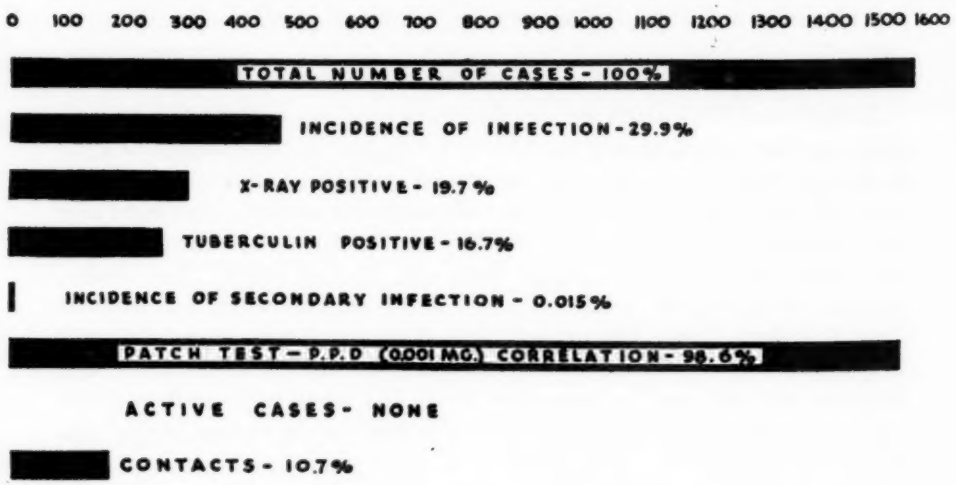
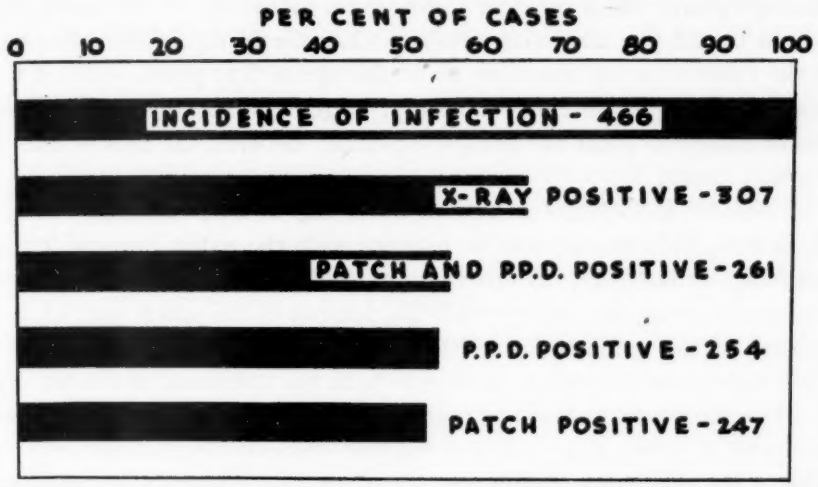
and Glover (1) found the patch test to give 7.0 per cent more positives than the Mantoux, in a younger age group. Fourteen individuals in the present series were negative to the patch test and positive to PPD, while 7 were positive to the patch test and negative to PPD. In active cases of pulmonary tuberculosis we have found the efficiency of both the patch test and PPD, 0.001 mg., to be equivalent. Two hundred and sixty-one of the 1,556, or 16.7 per cent, were positive to either or both tuberculins. Tuberculin testing alone would have missed 13.0 per cent, while X-ray alone would have missed 10.2 per cent of the positive cases (chart 1).


0 100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 1500 1600
TOTAL NUMBER OF CASES - 100%
INCIDENCE OF INFECTION - 29.9%
X-RAY POSITIVE - 19.7%
TUBERCULIN POSITIVE - 16.7%
INCIDENCE OF SECONDARY INFECTION - 0.015%
PATCH TEST - P.P.D (0.001 MG.) CORRELATION - 98.6%
ACTIVE CASES - NONE
CONTACTS - 10.7%

TUBERCULOSIS STUDY OF 1,556 HIGH SCHOOL FRESHMEN

CHART 1

Three hundred and seven of the total number tested, or 19.7 per cent, were positive by X-ray. Ninety-six (6.2 per cent) were positive to tuberculin and X-ray. Two hundred and five (13.2 per cent) were negative to both tuberculins and positive by X-ray. One hundred and fifty-nine (10.2 per cent) were positive to tuberculins and negative by X-ray. Three hundred and seven (65.9 per cent) of the total positive (466) in this series were positive by X-ray, while 261 (56.0 per cent) were positive to tuberculin, thus giving an increase in the efficiency of the X-ray over the tuberculins of 9.9 per cent. Previously (2) we found 15.0 per cent increased efficiency of X-ray over tuberculin in an age group of two to


PER CENT OF CASES
0 10 20 30 40 50 60 70 80 90 100
INCIDENCE OF INFECTION - 466
X-RAY POSITIVE - 307
PATCH AND P.P.D. POSITIVE - 261
P.P.D. POSITIVE - 254
PATCH POSITIVE - 247

RELATIVE EFFICIENCY OF X-RAY, P.P.D. AND VOLLMER PATCH TEST (LEDERLE)

CHART 2

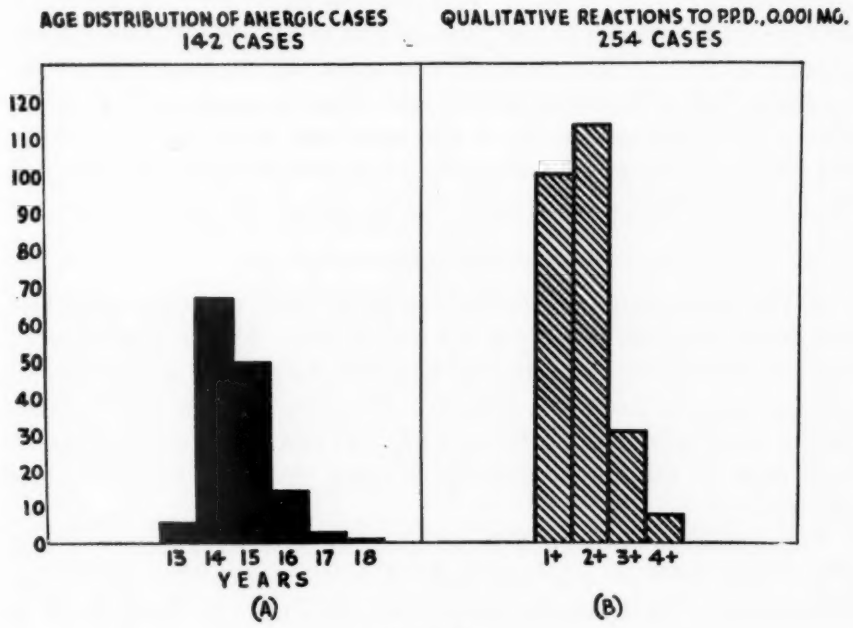


CHART 3

nineteen years. In a series of 1,000 adults (3) we found the tuberculin test to be 2.2 per cent more effective than the X-ray. The efficiency of the tuberculin test increases up to the age of fifty years, when it decreases due to probable loss of allergy. Age, however, does not explain loss of allergy in other age groups, especially between the ages of five to fourteen (chart 2).

Of the 205 individuals anergic to 0.001 mg. of PPD and the Vollmer patch test, 142 consented to be retested with the patch test and PPD, 0.005 mg. (chart 3A). Seven (4.9 per cent) gave a positive reaction. Five gave a one-plus reaction to PPD, but not to the patch test, while 2 reacted to the patch test and the second strength of PPD. These 2 previously gave a negative reaction to both the patch test and 0.001 mg. of PPD and seven weeks later were not only positive to the patch test, but gave a three- and four-plus reaction respectively to 0.005 mg. of PPD. By algebraic equation we, therefore, found that PPD 0.005 mg. would have an increased efficiency of 3.6 per cent over PPD 0.001 mg.

In considering qualitative reactions, the number of four-plus reactors in a previous study on 1,003 children (2) was 18.2 per cent with the second strength of PPD (0.005 mg.). In a previous report on 1,000 adults (3) we reduced the number of four-plus reactors to 5.0 per cent with the new strength of PPD (0.001 mg.). In this series, we obtained only 3.2 per cent of four-plus reactors with the new second strength of PPD (chart 3B). Of the 254 individuals in this series who were positive to PPD, 101 (39.7 per cent) gave a one-plus reaction, 114 (44.9 per cent) two-plus, 31 (12.2 per cent) three-plus and 8 (3.2 per cent) a four-plus reaction.

DISCUSSION

In this study there were 90 Negroes, 44 of whom had a positive patch test, which was read as easily as the test on white children. Of the total number (14) who were negative to the patch and positive to PPD, 5 were colored, whereas 9 out of a total of 1,446 white children were negative to the patch test and positive to PPD. If this is not a coincidence it may point to the impracticability of using the patch test on colored children.

Vollmer and Goldberger (4) found complete correlation in 89.0 per cent. They found 100.0 per cent conformity in a group of children with active tuberculosis. We agree with them that a skin test of 0.1 mg. of OT or less, or the first strength of PPD can safely be replaced with the patch test because of its greater efficiency. These same authors (5) used 1.0 per

cent solution of PPD on filter paper and also filter paper saturated with OT, so that both could be called patch tests. They believe OT is better because it contains more water, owing to its high content of hydrophile glycerin, whereas PPD is free from water until the moment of application.

Pearse *et al.* (1) found complete correlation between the Mantoux and patch test in 624 (492 negative, 132 positive) out of 712 tested, or 87 plus per cent. It must be noted that they compared the first strength of PPD with the patch test, and when it proved negative the second strength of PPD was used. In the present study, complete correlation was found between the patch test and PPD 0.001 mg. in 1,535 individuals out of 1,556 (1,295 negative, 240 positive), or in 98.6 per cent of the total number tested (table 1).

TABLE 1

Comparative results of tests on 1,556 high school freshmen

	VOLLMER PATCH TEST	PPD, 0.001 MG.	X-RAY
1,090	−	−	−
144	+	+	−
96	+	+	+
205	−	−	+
11	−	+	−
4	+	−	−
3	−	+	+
3	+	−	+
1,556			

Peck and Wegman (6) found only 30.0 per cent positive to PPD, first or second dose. They believe the patch test is unsuitable as a screening method. They quote Lumsden, Dearing and Brown (7) who noted variability between two brands of PPD, which might offer some explanation as to the discrepancy between their patch test results and those of other investigations.

Kerr and Winograd (8) obtained 98.0 per cent correlation (1,235 negative, 202 positive) out of 1,455 tested. They used the first strength of PPD. Taylor (9) found 94.0 per cent correlation out of 744 persons (511 negative, 191 positive) tested with 0.1 mg. of OT. This may point to various concentrations of tuberculin in different batches on patch tests. Since we found the patch test comparable to 0.001 mg. of PPD, we cannot account for the high correlation reported by the aforesaid authors (8 and 9) when they used the first strength of PPD and 0.1 mg. of OT. In

mass testing the patch test is not as economical as the Mantoux test, however in the office of the practicing physician the patch test is more economical and practical. If the patch test increases the use of tuberculin testing in private practice, its value is not only diagnostic, but educational, especially among a clientele that is skeptical of hypodermic injections. The patch test does not give so accurate a dosage for scientific research as an intracutaneous test, but present correlations demonstrate sufficient accuracy for general use.

SUMMARY

1. A total of 1,556 high school freshmen were tested simultaneously with the Vollmer patch test (Lederle), PPD and X-rayed. The incidence of infection, with the combined use of the tuberculins and X-ray, was found to be 30.0 per cent.

2. In this age group and locality the efficiency of the X-ray in finding lesions of pulmonary tuberculosis, over both PPD 0.001 mg., and the patch test, was 10.0 per cent. This strength of PPD found 3.0 per cent more positives than the patch test.

3. This intermediate strength of PPD (one-fifth the usual second strength) reduced the number of four-plus reactors to 3.0 per cent. Thirteen per cent were anergic to diagnostic doses of tuberculin; 142 of the 205 anergic individuals were rechecked. Ten per cent had masked or nonpulmonary type of lesions.

4. The Vollmer patch test is quite comparable to PPD, 0.001 mg. Ninety-eight per cent correlation was found between the two tests.

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THE VOLE ACID-FAST BACILLUS

I. Experimental Studies on a New Type of *Mycobacterium tuberculosis*

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The object of this paper is to report the results of experiments made to classify and study the vole acid-fast bacillus. This *Mycobacterium* is apparently a new type of the mammalian tubercle bacillus. It was discovered by Wells (1937) and causes an epizootic disease closely resembling tuberculosis in the wild English vole or field-mouse. Prior to this it had been stated that tuberculosis in warm-blooded animals living wholly in a wild state was unknown, Griffith (1930). This paper is an American report of the classification of this bacillus offered from an analysis of bacteriological and serological data.

Wells and Brooke (1940) have presented a preliminary report of experiments made to determine whether any immunity to experimental infection with virulent bovine and human tubercle bacilli is conferred on guinea pigs by vaccination with sublethal doses of the vole acid-fast bacillus. It was found that the vole acid-fast bacillus "gives a degree of protection which apparently is far greater than has been recorded by other means." These results were realized to be statistically insignificant, but sufficiently striking to warrant a preliminary report, especially as the war seriously interfered with the continuation of the experiments.

EXPERIMENTAL

A. *Studies on the Morphology, Staining, Acid-fastness and Resistance:* The *Mycobacterium* isolated from voles is a slender, nonmotile, pleomorphic organism whose sides are parallel to each other. It is longer in tissue than on Dorset's, Jensen's or Schwabacher's media. The average size (from over 1,000 individual measurements) in tissue is 3.6μ x .4μ while in culture the average size is 2.5μ x .4μ. Occasional forms which are oval or round are seen in most preparations. In certain lymph node sections long forms of the order of 8 to 10μ can sometimes be found. Thus the size of the organism roughly classifies it with the other pathogenic mycobacteria, although it seems to be slightly longer and thinner on the average than the fixed mammalian tubercle bacilli.

[1] Submitted as partial fulfillment of requirement for the degree of Ph.D., University of Oxford. Working now at Johns Hopkins Medical School, Baltimore, Maryland.

Five main forms exist in animal tissue: straight, S-shaped, hook-shaped, semicircular and circular. No true branching has been seen. Uneven staining predominates.

Figure 1 shows the vole acid-fast bacillus in the kidney of a rabbit. The bacilli had been introduced intravenously in large numbers some weeks before.

Figure 2 shows this bacillus in culture. Slightly curved, evenly-stained forms are numerous but one may always find the more pleomorphic forms also.

Figure 3 shows the pleomorphic condition in the localized focus of caseous pus from the guinea pig.

However, the vole bacillus could not be differentiated from the human or bovine tubercle bacillus by any method which had for its object the testing of the property of acid-fastness.

One finds it to be at least as resistant to 25 per cent sulphuric acid as, or possibly more so than, the human tubercle bacillus. The vole acid-fast bacillus also reacted to chloroform, sodium hydroxide and alcohols of various strengths in the same way as did the fixed mammalian tubercle bacilli.

Some experiments were performed to determine resistance to heat:

(*1*) Heat at 55°C. was not lethal to our strains even after thirty minutes.
(*2*) Heat at 60°C. was effective in killing all strains in from fifteen to twenty minutes.

In addition it was found that resistance to phenol and Dettol was the same apparently for the vole acid-fast bacillus as for the human and bovine tubercle bacilli.

B. *Cultural Reactions, and a Comparison of Growth upon Different Media:* The mycobacterium isolated from voles is an aerobic bacillus which grows slowly at temperatures from 36 to 38°C. However, no experiments have been carried out to determine the extreme range of temperatures at which growth may occur. Growth upon all media is slow, even slower than that of the fixed mammalian bacilli. Colonies may first become visible to the naked eye after from twenty to twenty-two days, but often one cannot find true colonies before six weeks. Some of the tiny colonies appearing first are hemispherical, transparent or translucent.

The bacillus grows on various egg media and often quite well on a 1 per cent glycerine serum agar. Liquid media such as Douglas potato, Sauton's, Dorset-Henley's or Long's are unsatisfactory. The organism

FIG. 1

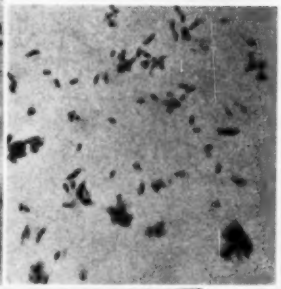


FIG. 2

FIG. 3

FIG. 4

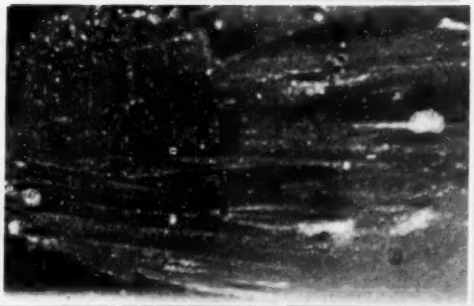
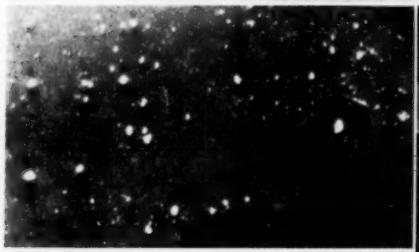


FIG. 5



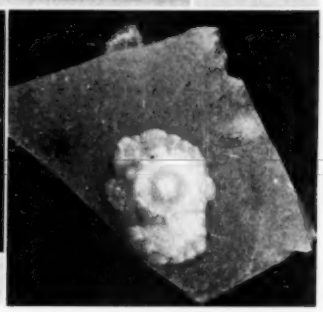


FIG. 6

FIGS. 1–6

is not enhanced in growth by glycerine but is somewhat inhibited by it. Colonies of primary and subculture will, however, appear on media containing small percentages of glycerine.

Perhaps the best way to illustrate the various kinds of colony formation is by the use of microphotographs.

Figure 4 illustrates a typical stroke culture.

Figure 5 illustrates the common type of colony appearing on Jensen's whole egg medium—a six weeks' growth.

Figure 6 illustrates a rough colony (enlarged) of an old culture, having been three months at 37°C. and fifteen months at 40°C.

Generally the consistency is that of cold lard. Often on drier media it is friable and on a moist medium in a young culture the consistency may be creamy.

A sweet, fruity odor is noticeable only in egg-medium bottles with an abundant growth. No odor is apparent in most of the dysgonic growths.

It was found that an egg-yolk normal saline medium (3:1) was the most suitable of the egg media for the growth of this vole bacillus. This statement is in reference to Loewenstein's, Jensen's, Dorset's and egg medium plus extract of *M. Phlei.* We found that 10 per cent carbon dioxide added to the atmosphere of incubation exerted a beneficial influence upon growth; 40 per cent oxygen inhibited growth.

C. *The Pathogenicity for Laboratory Animals:* The English and Continental field-voles have lately been used for typing human and bovine strains of the tubercle bacillus, Wells (1938), Griffith (1939). Both of these authors find the vole a better animal than the rabbit for this purpose because the vole reacts with lymph node caseation to avirulent as well as to virulent bovine strains, while human strains do not produce caseation.

Laboratory-bred voles were injected with graded doses of the vole acid-fast bacillus. These inocula ranged from 0.001 to 0.000,000,1 mg. and were given intraperitoneally. There were over 50 voles used in this experiment and macroscopical evidence of disease was found in every case upon necropsy at three and a half months. However, the slowness of this experimental disease is in distinct contrast to the rapid course caused in voles by the bovine tubercle bacillus, which results in extensive and progressive disease in three to four weeks.

The textbook picture of the typical tubercle is not commonly seen in the vole with natural or experimental disease. Usually the great multiplication of the bacilli obscures the small amount of cellular reaction.

One is impressed also with the amount of subcutaneous necrosis caused by the vole acid-fast bacillus in the vole if the inoculum is given subcutaneously. Here one is reminded of the leprosy bacillus and its action upon the human subcutaneous tissues.

It is impossible to give the details of our pathogenicity experiments in this short article. The summarized results of virulence tests upon the numerous rabbits were as follows:

1: The vole strain of acid-fast bacillus is less virulent for the rabbit than are the bovine and avian tubercle bacilli, and probably the human tubercle bacillus.
2: The rabbit responds to the vole strain with localized caseation and destruction of many bacilli. The disease is neither progressive nor fatal unless large doses are given intravenously.
3: In the guinea pig, of which almost 100 were used, the vole acid-fast organism produced much the same result. Subcutaneous injection of 0.001, 0.01, 0.1 and 1 mg. produces localized caseous lesions, but the disease is not progressive. The effect of larger doses is uncertain as yet.
4: In one rabbit an unusual lesion was found: caseation of the mammary tissue was present.
5: Instillation of thick suspensions of viable bacilli into the conjunctival sac produced no gross changes after six weeks; nor were gross changes found in guinea pigs six weeks after oral administration.

It is useful to tabulate our data to facilitate an understanding of the pathogenicity of the vole acid-fast bacillus in relation to some of the other closely related mycobacteria.

The virulence of some acid-fast organisms for various species of laboratory animals

TYPE OF TUBERCLE BACILLUS	RABBIT	GUINEA PIG	VOLE	FOWL	CALF	MONKEY	MOST COLD BLOODED ANIMALS
Human	x	xxx	x	0	x	xxx	0
Bovine	xxx	xxx	xxx	0	xxx	xxx	0
Avian	xx	0	x	xxx	x	x	0
Vole acid-fast bacillus	x	x	xx	0	x	?	?
Cold-blooded types of bacillus	0	0	0	0	0	0	xxx

xxx—The animal is highly susceptible to the bacillus which causes an acute, progressive disease in relatively small doses given subcutaneously.

xx—The animal shows chronic tuberculosis or slowly progressive and fatal tuberculosis, when moderate doses of the bacillus are inoculated subcutaneously.

x—The animal is very resistant to moderate doses of the bacillus, whose effects are generally restricted to the site of the subcutaneous inoculation. Sometimes massive doses by this route may cause death.

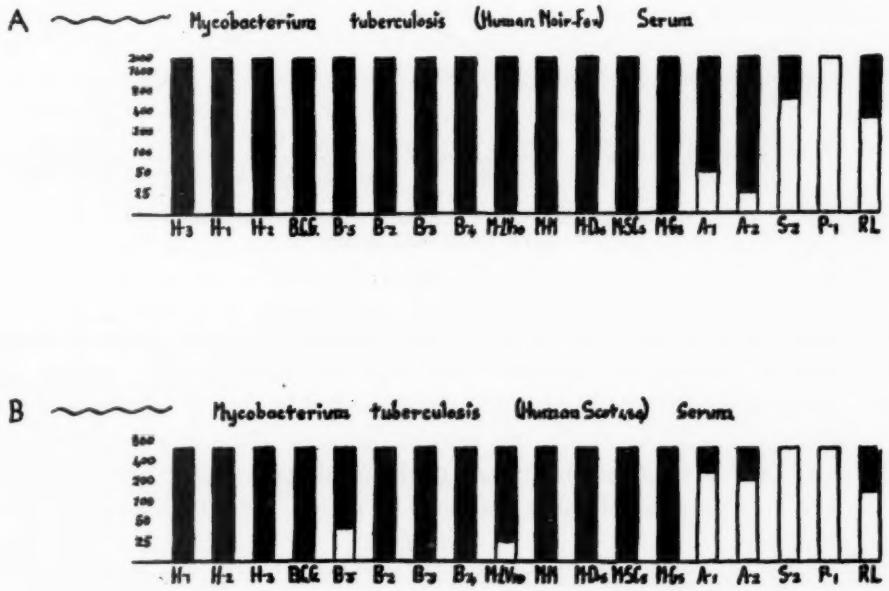
0—The animal is highly resistant to the bacillus which is incapable of producing generalized tuberculosis, no matter how large the dose.

D. *Serological Classification of the Vole Mycobacterium:* Extensive investigation of the serological properties of the vole acid-fast bacillus were undertaken. Seventeen antisera were prepared against various types of mycobacteria. Fifteen of these were monovalent and two were polyvalent. Absorption of agglutinins was the method used most widely and the method upon which most reliance was placed, although some direct agglutination experiments were completed. Wilson's (1925) article is especially relevant to the technique used throughout.

Again it is impossible to review the literature or describe in detail the method and results, which were recorded in chart form, one of which is shown here (chart V).

This symbolizes two antisera prepared against different strains of the human tubercle bacillus, absorbed with various mycobacteria and tested for agglutination again with the homologous agglutinating suspension.

Chart V Absorption of Agglutinins


A
Mycobacterium tuberculosis (Human Noir-Fou) Serum
H3 H1 H2 BCG B5 B2 B3 B4 MVo MM MDo MSGo MFo A1 A2 S2 P1 RL
B
Mycobacterium tuberculosis (Human Sart-14) Serum
H1 H2 H3 BCG B5 B2 B3 B4 MVo MM MDo MSGo MFo A1 A2 S2 P1 RL

Key: H—human tubercle, B—bovine tubercle, M—murine tubercle or the vole acid-fast bacillus, A—avian tubercle, S—smegma, P—phlei, and RL—rat leprosy absorptions.

The ordinate is the trace titre of the sera.

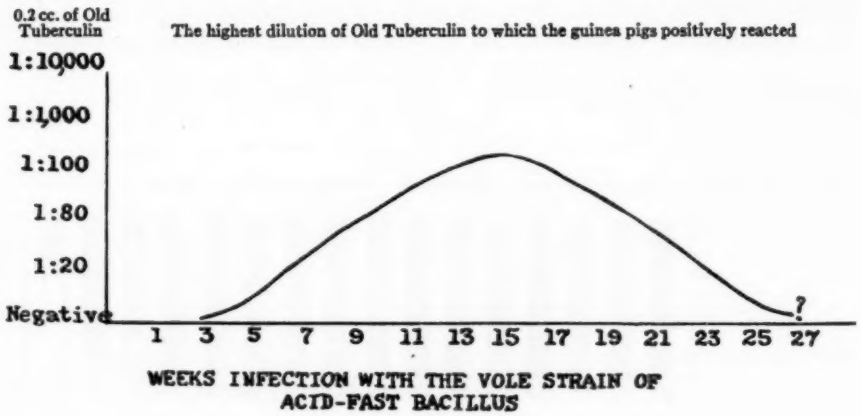
The rectangles are filled in solid with black if the strains in question were able to absorb all of the homologous agglutinins.

Summary of absorption of agglutinins:

1: No significant difference could be found between the vole acid-fast bacillus and the human and bovine fixed types of tubercle bacilli.
2: The vole acid-fast bacilli may be easily differentiated from the avian tubercle bacilli, rat leprosy, *M. phlei*, and *M. smegmatis*.
3: No evidence was found of a multiplicity of types among the vole strains.

Direct agglutination offers contributory evidence to the above conclusions which were reached by the absorption of agglutinins.

E. *Some Comparisons between the Skin Reactions Caused by a Vole Tuberculin and Old Tuberculin:* It is common knowledge that other myco-


0.2 cc. of Old Tuberculin
The highest dilution of Old Tuberculin to which the guinea pigs positively reacted
1:10,000
1:1,000
1:100
1:80
1:20
Negative
1 3 5 7 9 11 13 15 17 19 21 23 25 27
?
WEEKS INFECTION WITH THE VOLE STRAIN OF ACID-FAST BACILLUS

GRAPH 1

bacteria than the tubercle bacilli may sensitize the body tissues to mammalian tuberculin. Because the specific skin-reaction caused by tuberculin injection is generally recognized to be due to a protein, it was thought useful to study the relation between the protein of the vole acid-fast bacillus and the protein of the fixed mammalian tubercle bacilli. For this purpose the skin reactions of guinea pigs to tuberculins were tested.

The sensitivity of 52 guinea pigs vaccinated with the vole strain to Old Tuberculin was studied. In summary a composite picture of the average allergic state was obtained and recorded as a curve (graph 1). The curve represents the average of all guinea pigs.

A few of these guinea pigs were never positive to a dilution of tuber-

culin higher than 1:80; these animals were negative to a dilution of 1:20 after twenty-one weeks.

A few animals only reacted positively to a dilution of 1:1,000 at the fourteenth week; these were negative to a dilution of 1:20 at the twenty-sixth week.

A positive reaction to 0.2 cc. of OT intracutaneously was arbitrarily considered to be a pinkish flush with induration at least 10 mm. in longest diameter.

It is seen that these guinea pigs are most allergic to Old Tuberculin about three months after inoculation of the vole acid-fast bacillus; generally they fail to show any sensitivity until after the third week, and they are usually negative to the tuberculin after the sixth month, although atypical reactions sometimes occur.

The reactions of these same guinea pigs infected with the vole bacillus and tested with a tuberculin prepared from the vole bacillus were studied. Because this tuberculin was not prepared until the fifth month of this experiment, nothing was discovered about its reactions until then. It is interesting to note that between the fifth and seventh months after infection with the vole bacillus the animals were always positive to a 0.2 cc. dose of 1:20 dilution of vole tuberculin, but were generally negative to Old Tuberculin at this time.

In guinea pigs infected with human and bovine tubercle bacilli the vole tuberculin was always as effective as was Old Tuberculin in producing measured skin reactions.

From these experiments it seems that the Vole Tuberculin possesses a group and a specific protein, the latter not possessed by Old Tuberculin. Thus these biological tests indicate a chemical difference between the vole and fixed mammalian tubercle bacilli—a difference not brought out by serological methods.

In conclusion, it may be mentioned that numerous animals were tested with Purified Protein Derivative, but no significant difference was noted between this substance and Old Tuberculin.

DISCUSSION

Suggested Name for the Vole Acid-fast Bacillus "Mycobacterium Tuberculosis Var. Muris"

The evidence obtained from this and other experimental work suggests that the vole acid-fast bacillus is a type of mammalian tubercle bacillus. Admittedly, there are two findings which indicate that the vole strain

has some similarity to the leprosy bacilli: (*a*) the slowness of growth and its dysgonic nature, and (*b*) the formation of subcutaneous lesions after subcutaneous inoculation of the vole strain into the vole. However, (*a*) is not a constant finding and these considerations are minor factors when they are weighed against the data which classify the vole acid-fast bacillus as being a type of tubercle bacillus; but it is well to realize that the vole acid-fast bacillus may be considered as a link between the leprosy and the tubercle types of mycobacteria. When and if the study of rat and human leprosy reaches a stage consistent with significant antigenic analysis, then further comparative statements can be made.

The evidence for suggesting that the vole acid-fast bacillus is a mammalian type of tubercle bacillus is briefly reviewed as follows:

A: The bacillus is the cause of an epizootic disease in a few species of small mammals, the field-vole (*Microtus agrestis*) and the bank-vole (*Clethrionomys glareolus*). This disease closely resembles tuberculosis. Involvement of the organs is common and tubercle formation may be seen in early disease of the spleen and liver.

B: After analyzing the antigenic structure by the absorption of agglutinins the writers have concluded that the vole strains could not be differentiated from the bovine and human tubercle bacilli by this method. In addition, the vole strains which were used were approximately the same, because they presented no wide range of antigenic structure within the type.

(*1*) The vole strain could easily be differentiated from the saprophytic acid-fast bacilli and from the avian tubercle bacilli and a suspension of the tissue from a heavily infected case of rat leprosy. The writer makes no claim that this latter finding is infallible. However, no other way than to use a tissue suspension is so suitable if one wishes to study the rat leprosy bacillus serologically; the suspension was seen microscopically to consist of almost pure bacilli.

C: A study of the pathogenicity of the vole strain shows that it is avirulent for guinea pigs and rabbits in moderate doses, but may sometimes be fatal in larger doses. In this respect its virulence is less than that of the fixed mammalian strains, but more than the leprosy types of mycobacteria. However, definite caseous necrosis is formed locally and giant cell systems may form in the liver, spleen and lung.

D: The cultural reactions of the vole strain are not inconsistent with a classification of this bacillus as a type of tubercle bacillus. Slowness of growth on egg media, production of raised, dry, waxy or crumbly colonies and a dysgonic kind of growth are characteristics of other strains of the fixed mammalian tubercle types. These cultures all cause progressive disease in the vole; thus they may not be likened to many of the so-called leprosy bacilli which fail to satisfy this postulate of Koch.

E: Morphologically the vole strain does not resemble any of the known, pathogenic acid-fast organisms, for it has hooked, semicircular and S-shaped forms in tissue. However, this pleomorphism indicates that it is more like the avian tubercle bacillus in this respect than the rat leprosy bacillus.
F: Acid-fastness and staining properties of the vole strain are entirely consistent with its being a tubercle bacillus.
G: Allergic phenomena as studied by the use of a Vole Tuberculin and a mammalian tuberculin indicate a strong degree of similarity between the vole strain and the mammalian tubercle bacilli. Old Tuberculin may give positive reactions in 1:100 dilution in guinea pigs infected with the vole strain, and Vole Tuberculin may give positive reactions with the same dilution in guinea pigs infected with human or bovine tubercle bacilli.
H: Protection against experimental tuberculosis of human or bovine type in the guinea pig is given by vaccination of the guinea pig with the vole strain of acid-fast bacillus. This induced immunity is another indication of the probable similarity between the vole strain and the fixed types of mammalian tubercle bacilli.

Before classifying the vole strain as another type of tubercle bacillus, it is necessary to indicate in what ways it is different from the types listed in Topley and Wilson (1936) and Bergey (1934).

Pathogenicity tests are most helpful for this purpose. In the rabbit, for example, which is used for differentiating an unknown tubercle bacillus, 10 mg. of the vole strain given subcutaneously and 1 mg. intravenously show that it is not a virulent bovine or avian type. Next it must be differentiated from the human type; the guinea pig is a suitable animal for this purpose, and 1 mg. subcutaneously of the vole strain shows that it is not a virulent human type. Another way of proving this difference between the vole strain and the other tubercle bacilli is the vole test, (see Wells, 1938).

Morphologically the vole strain is different from any of the previously described tubercle bacilli; hook-shaped, S-shaped, circular and semicircular forms are not characteristic of any other tubercle bacillus.

The presence of the epidemic disease in wild field-voles in regions fenced off from domesticated animals offers an argument against its aetiological agent being a tubercle bacillus of bovine or human origin.

These and numerous other less important reasons show clearly that the vole strain is a distinct type of tubercle bacillus, although it may not be differentiated from the human and bovine types by serological methods.

Proof that it is not a Johne bacillus is offered from the unpublished

evidence of Wells and Brooke, 1939, in which it is shown that various strains of typical Johne bacilli will not cause progressive disease in the field-vole.

The writer, therefore, suggests the name *Mycobacterium tuberculosis* variety *muris* (after Bergey's nomenclature) for the vole type of acid-fast bacillus.

The writer would express his gratitude to the British Medical Research Council and the Cecil Rhodes Scholarship Trust for the financial aid extended to this work. He would also acknowledge the assistance of Dr. A. G. Saunders, Mrs. G. O'Conor and Mrs. J. Chapman.

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THE CARBOHYDRATE CONTENT OF THE PROTEINS IN BLOOD SERUM, CANTHARIDIN BLISTERS AND PLEURAL EFFUSIONS[1]

B. LUSTIG AND E. NASSAU

Investigations of the carbohydrate content of the isolated serum proteins have already provided useful data in respect to their composition under normal and pathological conditions.

In the present study, determinations of the carbohydrate content have been utilized in an examination of the alterations suffered by proteins of blood serum and pleural exudates in cases of pneumothorax pleurisy.

The nature of the carbohydrate component of the serum proteins has been elucidated by the work of Rimington (1) (1930) and Bierry (2) (1930) who from serum proteins obtained a glucosamine-galactose-mannose complex. Lustig (3) and his coworkers (1930) showed that the serum globulins are richer in carbohydrate than the albumins; Hewitt (4) (1936) obtained from serum albumin a fraction which was practically carbohydrate-free.

Lustig and Langer (5) (1931) have described a method based upon the colorimetric procedure of Tillmanns and Philippi (6) (1928), which they have used for determination of protein sugar in normal and various pathological sera. By simultaneous determination of the protein nitrogen and calculation of the "carbohydrate index" (C.I.) or ratio of protein sugar to protein nitrogen according to Lustig and Ernst (7) (1937), differences in protein composition are more sharply characterized. Examination of arterial and venous blood from the same individual by Lustig, Leiner and Ernst (8) (1937) revealed in 66 per cent of the cases a higher protein content in arterial blood sera; the carbohydrate content, however, was higher (in 85 per cent of cases) in the serum proteins in venous blood. It would appear that during the passage from arterial to the venous system, there must be an absorption by the tissues of proteins of lower carbohydrate content and a replacement of the latter by proteins rich in carbohydrate.

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In the present investigation, the method of Lustig and Ernst (7) (1937) has been employed. Four portions, 0.1 cc. each, of serum were diluted five fold with water, 5 cc. alcohol were added and the precipitates were collected by centrifuging. Each was purified by boiling with 5 cc. of alcohol and again centrifuged. Total nitrogen was determined in two samples by the micro-kjeldahl method and protein was calculated by the use of the factor 6.25. The precipitates of the remaining two tubes were dissolved in 0.4 cc. of 1 per cent sodium hydroxide and 0.2 cc. of 2 per cent orcinol in 25 per cent sulfuric acid was added and then 6 cc. of 60 per cent sulfuric acid. After ten minutes heating in the boiling water bath they were cooled by tap water, diluted to 20 cc. with 60 per cent sulfuric acid and compared colorimetrically with standard glucose solutions similarly treated. The concentration of acid and time of heating must be strictly observed and the tubes protected from direct daylight. The acid-orcinol sulution should be stored in the dark and rejected if it acquires a pinkish brown tint (Rimington (14)).

Blood, pleural fluid and the exudate from a cantharidin blister were removed at the same time for examination. The exudates were centrifuged before analysis and their small fibrinogen content ignored. The blood sera were allowed to separate in the ice chest and any showing marked haemolysis were discarded. Several determinations of free sugar showed that there was no relation between this and the protein sugar content.

The technique of the cantharidin blister was introduced by Kauffmann (9) (1923) in a study of inflammation. Kauffmann (1923), Markees (10) (1935) and others (11) have evaluated the tendency of the organism to inflammatory response by means of the cell picture and the determination of the free sugar in the content of such blisters and in the blood serum. In normal individuals there is a constant picture and a definite relation between these two free sugar values but in different pathological conditions characteristic deviations are observable. No further data, for example, protein content, are available for cantharidin blister fluids.

In our experiments, a 1 cm.^{2} cantharidin plaster was fixed with adhesive plaster to the calf of the leg for twenty-four hours. The blister was then carefully cut with scissors at one corner, the content (0.5 to 1.0 cc.) collected in a small centrifuge tube and the protein nitrogen and protein sugar determined. It was to be expected that local changes in permeability would be reflected in alterations of total protein and globulin content in the exudates as compared with the blood serum.

A comparison of protein nitrogen and protein sugar in blood serum and cantharidin blister exudate of 7 normal males is presented in table 1.

The protein content of the cantharidin blister fluid as compared with the blood serum is 20 to 50 per cent lower. The carbohydrate content of the isolated proteins of the former is also considerably lower than that of the blood serum proteins, pointing to a higher albumin-globulin ratio in the blister fluid than in the serum.

TABLE 1

NUMBER SIGN	MATERIAL	NITROGEN	PROTEIN	PROTEIN SUGAR	CARBOHYDRATE CONTENT OF THE PROTEINS	CARBOHYDRATE INDEX
		mg. per cent	*per cent*	*mg. per cent*	*per cent*	
(1) EN	Blood serum	1,150	7.20	135	1.88	8.50
	Blister fluid	840	5.25	83	1.58	10.10
(2) NE	Blood serum	1,230	7.69	109	1.42	11.31
	Blister fluid	988	6.18	68	1.10	14.50
(3) RN	Blood serum	1,250	7.81	155	1.98	8.04
	Blister fluid	620	3.88	75	1.94	8.27
(4) OK	Blood serum	1,420	8.88	104	1.17	13.66
	Blister fluid	1,146	7.17	69	0.96	16.61
(5) EF	Blood serum	1,260	7.88	131	1.66	9.61
	Blister fluid	880	5.50	68	1.24	12.94
(6) MB	Blood serum	1,250	7.81	122	1.56	10.25
	Blister fluid	880	5.50	72	1.31	12.22
(7) MLR	Blood serum	1,120	7.00	122	1.74	9.18
	Blister fluid	920	5.75	61	1.51	10.61

The pneumothorax exudates and cases of exudative pleurisy, next investigated, were classified according to their cytological and bacteriological characteristics (Dissmann and Nassau 1938 (12)) as follows:

1: Small effusions, in general culturally sterile and eosinophile, unaccompanied by general reactions, such as fever and not affecting the blood sedimentation rate. These may be regarded as allergic exudates of a local nature.

2: Rapidly increasing large effusions, containing lymphocytes and from which tubercle bacilli generally may be cultured. These are usually accompanied by fever, an increase in blood sedimentation rate and severe general reaction. They are to be regarded as true inflammatory exudates of tuberculous nature.

Table 2 includes 7 cases of fresh, sterile, eosinophile mostly spontaneously and rapidly absorbed effusions. The blood serum of all these cases showed a normal protein content and an elevated protein-carbohydrate content. A raised bound-sugar value has been reported by previous authors (Grevenstuck (13), Lustig and Langer (5)) in many diseases and particularly in tuberculosis. The protein content of pneu-

TABLE 2

NUMBER SIGN	MATERIAL	NITROGEN	PROTEIN	PROTEIN SUGAR	CARBOHYDRATE CONTENT OF THE PROTEIN	CARBOHYDRATE INDEX
		mg. per cent	*per cent*	*mg. per cent*	*per cent*	
(1) EN	Blood serum	1,148	7.17	302	4.21	3.76
	Blister fluid	945	5.90	228	3.82	4.14
	Pleural effusion	924	5.77	212	3.85	4.38
(2) HA	Blood serum	1,274	7.96	267	3.40	4.77
	Blister fluid	728	4.55	179	3.94	4.61
	Pleural effusion	687	4.29	167	3.89	4.11
(3) BJ	Blood serum	1,120	7.00	190	2.71	5.89
	Blister fluid	691	4.32	127	3.01	5.44
	Pleural effusion	735	4.59	115	2.51	6.39
(4) KE	Blood serum	1,211	7.56	235	3.11	5.10
	Blister fluid	810	5.07	158	3.11	5.10
	Pleural effusion	861	5.38	168	3.11	5.10
(5) LO	Blood serum	1,288	8.05	220	2.73	5.85
	Blister fluid	728	4.55	141	3.09	5.16
	Pleural effusion	735	4.59	118	2.57	6.23
(6)	Blood serum	1,274	7.96	246	3.09	5.18
	Blister fluid	875	5.46	154	2.87	5.67
	Pleural effusion	672	4.20	196	4.67	3.43
(7)	Blood serum	1,120	7.00	226	3.23	4.95
	Blister fluid	770	4.81	158	3.28	4.87
	Pleural effusion	700	4.37	173	3.96	4.05

mothorax effusions and cantharidin exudates were similar and lower than that of the blood serum. The carbohydrate content of these proteins was found to be the same or even higher than that of the blood serum, whereas it has already been pointed out that in normal individuals the protein carbohydrate content of the exudates is much lower than that of the blood serum proteins.

With clinical improvement (absorption of the exudate) there occurred a decrease in the total protein sugar of the blood serum and also of the carbohydrate content of the serum proteins with a corresponding increase in the carbohydrate index which followed very closely the alteration in sedimentation rate.

In table 3 are reported 6 cases of fresh pneumothorax effusions, containing both lymphocytes and bacteria. In one case (no. 6) the protein-

TABLE 3

NUMBER SIGN	MATERIAL	NITROGEN	PROTEIN	PROTEIN SUGAR	CARBOHYDRATE CONTENT OF THE PROTEIN	CARBOHYDRATE INDEX
		mg. per cent	*per cent*	*mg. per cent*	*per cent*	
(1) MJ	Blood serum	1,148	7.17	251	3.50	4.57
	Blister fluid	798	4.98	165	3.31	4.84
	Pleural effusion	701	4.38	219	4.00	3.20
(2) AI	Blood serum	1,106	6.91	232	3.36	4.77
	Blister fluid	770	4.81	147	3.06	5.24
	Pleural effusion	721	4.50	189	4.20	3.81
(3) JF	Blood serum	1,253	7.83	240	3.07	5.23
	Blister fluid	837	5.23	166	3.17	5.02
	Pleural effusion	840	5.25	210	4.00	3.99
(4) LA	Blood serum	1,316	8.22	260	3.16	5.06
	Blister fluid	945	5.90	187	3.15	5.05
	Pleural effusion	910	5.68	161	2.83	5.65
(5) BG	Blood serum	1,214	7.61	286	3.76	4.24
	Blister fluid	994	6.21	259	4.17	3.83
	Pleural effusion	938	5.86	202	3.45	4.69
(6) PJ	Blood serum	1,120	7.00	335	4.78	3.34
	Blister fluid	751	4.69	165	3.52	4.55
	Pleural effusion	826	5.66	187	3.30	4.41

carbohydrate content of both pleural exudate and cantharidin exudate was similar but lower than that of the blood serum proteins.

The examination of cases of bacillary effusions of from four to six months standing (table 4) showed in exudate and in blister fluid in all cases a protein-carbohydrate content higher even than that of the blood serum which was itself raised above the normal level. While in healthy individuals the protein-carbohydrate content of the blood serum was always

higher, all cases of tuberculosis evinced, according to the intensity of the disease, a relatively higher protein-carbohydrate content in the cantharidin exudate than in blood serum (tables 2 to 4). A striking feature of the results shown in table 4 is the fact that in these cases the newly produced cantharidin exudate gave figures for carbohydrate content and

TABLE 4

NUMBER SIGN	MATERIAL	NITROGEN	PROTEIN	PROTEIN SUGAR	CARBOHYDRATE CONTENT OF THE PROTEIN	CARBOHYDRATE INDEX
		mg. per cent	*per cent*	*mg. per cent*	*per cent*	
(1) P	Blood serum	1,330	8.31	314	3.78	4.23
	Blister fluid	875	5.46	262	4.79	3.33
	Pleural effusion	744	4.65	233	5.01	3.19
(2) LE	Blood serum	1,330	8.31	214	2.57	6.21
	Blister fluid	889	3.55	216	3.89	4.10
	Pleural effusion	980	6.12	235	3.83	4.17
(3) PV	Blood serum	1,232	7.70	296	3.84	4.14
	Blister fluid	707	4.41	194	4.40	3.64
	Pleural effusion	896	5.60	263	4.69	3.40
(4) KW	Blood serum	1,260	7.87	225	2.88	5.57
	Blister fluid	700	4.37	190	4.34	3.69
	Pleural effusion	742	4.63	195	4.21	3.78
(5) WG	Blood serum	1,330	8.31	284	3.41	4.68
	Blister fluid	882	5.51	223	4.05	3.95
	Pleural effusion	728	4.55	187	4.11	3.84
(6) NB	Blood serum	1,218	7.61	279	3.67	4.36
	Blister fluid	824	5.15	166	3.22	4.96
	Pleural effusion	770	4.81	176	3.65	4.37
(7) NF	Blood serum	1,260	7.87	227	2.89	5.55
	Blister fluid	819	5.11	209	4.08	3.92
	Pleural effusion	868	5.42	218	4.02	3.98

carbohydrate index very similar to those of pneumothorax exudates of long standing but differing considerably from the figures for the blood serum. There must, therefore, have been in these cases a profound alteration in the conditions governing the permeability for proteins. As a consequence of this conclusion, the view that alterations in the composition of old exudates (for example, increase in globulin content) are due

to mechanical factors, such as thickening of the pleura, must be rejected in favor of the explanation that there occurs an alteration in permeability relationship throughout the organism. In respect to the protein-carbohydrate, the protein distribution in exudation fluid is the same whether the exudate be of long standing (pleural effusions) or freshly produced (cantharidin blister fluid). That the actual protein-carbohydrate figure is higher than in blood serum suggests the passage of tissue proteins into the exudate.

By the same methods, 2 cases of exudative pleurisy accompanying pulmonary tuberculosis have been examined (table 5). In case 1 there was in addition to the pleurisy an extensive and progressive fibrocaseous pulmonary tuberculosis. Although the protein-carbohydrate content

TABLE 5

NUMBER SIGN	MATERIAL	NITROGEN	PROTEIN	PROTEIN SUGAR	CARBOHYDRATE CONTENT OF THE PROTEIN	CARBOHYDRATE INDEX
		mg. per cent	*per cent*	*mg. per cent*	*per cent*	
(1) ZJ	Blood serum	1,204	7.52	299	3.96	4.02
	Blister fluid	840	5.25	255	4.85	3.29
	Pleural effusion	826	5.16	232	4.49	3.55
(2) CM	Blood serum	1,134	7.08	215	3.03	5.27
	Blister fluid	728	4.55	144	3.17	5.06
	Pleural effusion	832	5.20	202	3.88	4.11

of the blood serum was very high, this figure was still exceeded by those of the cantharidin and pleural exudates. The second case, of unilateral, quiescent pulmonary tuberculosis, exhibited the same carbohydrate content and carbohydrate index in blood serum, pleural and cantharidin exudates. Investigations upon individual cases, repeated at intervals, showed that clinical improvement was accompanied by a decrease in the carbohydrate content of the blood serum; such a change may be interpreted as a favorable prognostic sign. Free sugar determination showed, as usual, no relation to the protein sugar.

SUMMARY

The nitrogen and carbohydrate contents of the proteins of the blood serum and cantharidin and pleural exudates have been determined in cases of pulmonary tuberculosis in the pneumothorax effusion and exudative pleurisy.

Similar determinations have been made upon blood serum and cantharidin blister fluid of normal individuals.

In normal individuals the carbohydrate content of the total proteins of the cantharidin exudate is lower than that of the blood serum.

In tuberculosis, there was found an increase in the protein-carbohydrate content of the cantharidin exudate, the extent of this increase corresponding approximately to the severity of the disease. Determinations of the protein-carbohydrate content of the serum may be of prognostic value in tuberculosis.

In patients with pneumothorax effusions and exudative pleurisy of long standing, the carbohydrate contents of the isolated total proteins of the pneumothorax exudate and freshly induced cantharidin blister fluid are identical or closely similar and higher than that of the blood serum.

On this account it must be concluded that the alterations in protein composition of bacillary pneumothorax exudates of long standing are not due to local conditions affecting permeability but to alterations affecting the permeability of the tissues throughout the entire organism. There also appears in these cases to be an influx of relatively carbohydrate-rich tissue proteins into the exudates.

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COMPLEMENT FIXATION IN TUBERCULOUS DOGS[1,2]

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The complement fixation test has been widely employed as an aid in diagnosis of human tuberculosis but with only a limited degree of success. It has also been used in investigations of antibodies in experimental tuberculosis. The purpose of this paper is to report the results of complement fixation tests and to attempt to correlate them with other findings in experimental pulmonary tuberculosis in the dog.

TECHNIQUE OF COMPLEMENT FIXATION TEST

Antigens: Five antigens were used during the period of investigation. Antigens IA and IB were prepared in the same way. A mixture of human and bovine strains of the tubercle bacillus, grown on Herrold's medium, was suspended in physiological salt solution with the aid of a mechanical shaker, then heated to 60°C. for thirty minutes and 0.5 per cent phenol added. Antigen J was similarly made except that the bacilli were cultured on a synthetic medium. Antigen II differed from IA in that the mixture was suspended by grinding in a mortar with salt solution and bile. Antigen L, a bovine strain, was suspended after the growth had been lyophilized. PPD (Seibert) was tried as an antigen, but such low readings were obtained that it was soon discarded. Most of the sera were also tested with a cholesterinized Wassermann antigen.

The effect of lecithin on antigen J was studied. However, the amount of lecithin necessary to augment fixation in the presence of complement was sufficient to produce haemolysis in the absence of complement. The presence of small amounts of guinea pig or dog serum inhibited the lecithin haemolytic activity as well as its ability to increase fixation. False reactions tended to occur, consequently lecithin reinforcement was not practiced.

The antigens were titrated for anticomplementary properties every few weeks. Approximately one-fourth of the anticomplementary dose (in 0.1 cc.) was used in the tests. The antigenic unit was determined when strongly posi-

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[2] Aided by a grant from the Committee on Scientific Research of the American Medical Association.

tive sera were available. The range between the anticomplementary dose and antigenic unit was sufficient to permit the use of one-fourth the anticomplementary dose, which was still at least two to three times the antigenic unit.

A series of antigen preparations was used, two antigens at a time, in such a way that when one was exhausted a second was still available for comparison with a third which was being used to replace the first. The average of all titres obtained with each antigen was approximately the same. The potency of the antigens was compared by the following procedure. Whenever a given pair of antigens was used to test the same sera, the end-titres obtained with each antigen were compared. On this basis antigen II was weaker than IA; IA was slightly weaker than IB; IB was about the same as L; and IB was weaker than J. IA and II, however, were prepared three and a half months before IB and L, and IB and L were prepared six months before J. Thus much of the time an older antigen was being compared with a newer one, and their comparative ages brought out by their relative potencies. Therefore, because we had no unchanging standard, and because all antigens seemed to lose potency, the highest titre of any antigen used on each serum was considered in interpreting results. The end-titre chosen was that in the tube with the highest dilution showing 2+, 3+ or 4+ fixation.

In graphing the results, average titres of 0–1 were plotted as 0, because the scale is logarithmic.

Sera: Sera were inactivated by heating for thirty minutes at 56°C. and usually tested within twenty-four hours of their collection. In the test the sera were used in 0.1 cc. amounts beginning with undiluted serum and doubling the dilution in each succeeding tube. Control tubes included positive serum, negative serum, anticomplementary control, native amboceptor control and cell suspension control. If the control for native sheep amboceptor was positive, the complement fixation test was repeated after absorption of the native amboceptor with sheep cells. Sixty-two per cent of the tuberculous dogs exhibited native amboceptor at some time but it was not always found in a given dog. Fifty-seven per cent of the normal dog sera tested showed native amboceptor. The removal of the native amboceptor seemed to have little effect on the titre of the serum.

Complement: Two units of guinea pig complement in 0.1 cc. were used. This amount was usually contained in a 1:10 dilution.

Haemolytic amboceptor and cell suspension: Two units of amboceptor were employed. When the experiment was begun amboceptor was used in 0.1 cc. amounts. Later the two units of amboceptor in 0.2 cc. amounts were added to the cells for preliminary sensitization at 37°C. for thirty minutes.

Sheep red blood cells were used for four days and washed each day just before using. At first 1 cc. of a one per cent suspension was used but when sensitized cells were utilized 0.2 cc. of a 5 per cent suspension was employed.

In the test, the mixture of antigen, serum and complement was incubated in a water bath at 37°C. for one hour, the indicator system added and incubation continued one-half hour. The mixture was then placed in the icebox to be read the following morning.

TECHNIQUE OF OTHER PROCEDURES

The dogs were infected intrabronchially unless otherwise stated. The technique of injection (1) makes use of a special bronchoscope with side tube which accommodates a urethral catheter through which suspensions of tubercle bacilli in saline or mucin are injected. The bacillary suspensions were measured by centrifugation of suspensions in Hopkins tubes. X-ray films were made of the dogs on a special table which holds them in a supine position.

The skin tests herein considered were made with 0.1 cc. of 1:100 OT injected intracutaneously. Tests were done with other dilutions and with PPD, but 1:100 OT was used most frequently (2). The method of grading is that of Aronson (3).

RESULTS

Fixations in normal dogs will be considered first and then fixations in tuberculous dogs will be reported according to size of dose, type of infection, X-ray findings, results of skin tests and postmortem findings. Most of the tuberculous dogs had been studied prior to infection as normal dogs.

Normal dog sera: Titrations were run throughout the period of study on sera from normal dogs as they came from the pound. The results are given in table 1.

With the five different antigens, 76 complement fixation tests were run on 43 sera from 25 dogs. With the exception of one serum (that mentioned in footnote 2 of table 1) complete fixation was observed in a titre of 1:2 only once, and in undiluted serum 6 times. With the exception of the same sample 2 to 3 + fixation was seen in a titre of 1:5 twice, in a titre of 1:2 ten times and in undiluted serum 20 times. Apparently then, complete fixation in a titre of 1:2, or 2 to 3 + fixation in a titre of 1:4 is of some significance in tuberculous dogs, and titres higher than this are of considerable significance. Whether any of these "normal" dogs had ever been infected with tuberculosis previous to experimental handling we are not able to say. Dogs which recover from experimental infections tend to lose complement fixation antibodies but maintain positive skin tests for at least a year. Since none of these normal dogs gave positive skin tests, the single high fixation is apparently nonspecific.

The Wassermann antigen invariably gave negative results.

Size of dose: The data were first studied to determine whether there were any differences in titres when different doses of tubercle bacilli were used. The doses fell most conveniently into three groups: (*a*) less than 1 mg. (*b*) approximately 1 mg. and (*c*) over 1 mg. In the first group there were 23 observations on 9 dogs, in the second group 59 on 25 dogs and in the third, 99 on 25 dogs. The results are presented in table 2 and chart 1. As can be seen, there are no consistent differences between the averages. Statistics obtained in comparison of the means by the "t" test (4) are given. They show no significant differences.

TABLE 1

Complement fixation in sera of normal dogs

	ANTIGEN					TOTAL
	IA	II	IB	L	J	
	Total number of samples					
	21	12	27	9	7	76
Number showing complete fixation in 1:1 dilution	2	2	2*	0	2*†	8
Number showing complete fixation in dilution greater than 1:1	0	0	1*	0	2*†	3
Number showing 2–3+ fixation in 1:1 dilution	7	2	5	4	1	20
Number showing 2–3+ fixation in 1:2 dilution	5	2	2	1	0	10
Number showing 2–3+ fixation in dilution greater than 1:2	1‡	1‡	1*	0	1*	4

* One serum gave complete fixation in a titre of 1:2 with both antigen IB and J, and 2–3+ fixation in a titre of 1:4 with IB and 1:8 with J. A repeated test on the same sample confirmed the results.

† One serum fixed completely in a titre of 1:2.

‡ One serum gave 2–3+ fixation in a titre of 1:5.

For all doses the average began to rise in the first five days and reached a maximum of 30–40 at ten to forty days after which time there was a slow falling off. After one hundred days the decrease seemed slight or negligible but the number of observations is small.

Type of infection: There were four types of infection: primary with virulent strains; reinfection with virulent strains; intravenous BCG; virulent infection after BCG. In the first group there were 105 observations on 38 dogs; in the second, 40 on 14 dogs; in the third, 24 on 5; in the fourth, 40 on 11 dogs. The results are presented in table 3 and chart 2. Examination of the table shows a tendency for reinfections to

have higher titres, especially after primary infections with virulent bacilli. To assess the significance of these differences the "t" test was again used. First, each column was compared with the average of all samples (table 2, column 5). The statistics obtained are given at the bottom of table 3 ($\bar{x}$ = the mean difference between the columns compared, t is a measure of the spread of the differences, $n = n'-1$, where n' = the number of differences, and P = the probability that the differences are explainable by chance). The results following intravenous BCG infection differ significantly (from the average of all samples), primary infections with probable significance, and reinfection and infection after BCG without significance. Although the mean difference between reinfection and all samples is great, the single unusually large value throws question on the significance of the difference. Next, reinfection was compared with primary; a greater mean difference was

TABLE 2

Size of infecting dose and average complement fixation titre

DAYS	DOSE			TOTAL
	< 1 mg.	ca. 1 mg.	> 1 mg.	
0–4	0	24.2	9.3	10.8
5–9	1.2	46.7	39.2	26.3
10–19	80.0	32.0	45.7	45.4
20–29		20.9	64.0	25.2
30–39	32.0	35.0	24.0	27.1
40–49		19.1	12.0	15.6
50–59	16.0	9.8	29.0	22.6
60–69	8.0	1.5	4.0	3.0
70–79		64.0	8.0	22.0
80–89		6.5	15.75	13.9
90–99			8.0	8.0
100–139	0.7	0	4.0	1.6
140–179		4.0	4.5	4.3
180–219		4.5		4.5
220–299	3.0	0	8.4	6.0
300–379		2.4	4.0	2.7
380–459		10.0		10.0
460–539		0		0
Difference from total	n = 7 t = .02 m = +2.9 P > 0.9	n = 16 t = 0.90 m = +2.9 0.4 > P > 0.3	n = 14 t = 0.37 m = −0.14 0.8 > P > 0.7	

found, and the significance of the difference became greater. Finally the primary infections were compared with all samples in the first one hundred days, and the difference was found to be of high significance.

The data may be summarized as follows: In previously uninfected dogs virulent strains produced a higher antibody titre than did BCG. Dogs which had been infected primarily and secondarily with virulent strains showed higher titres than did dogs which had been infected primarily with BCG and secondarily with virulent strains. The differences were greatest in the first forty to sixty days, the period of maximum antibody titre. Intravenous BCG gave a type of antibody

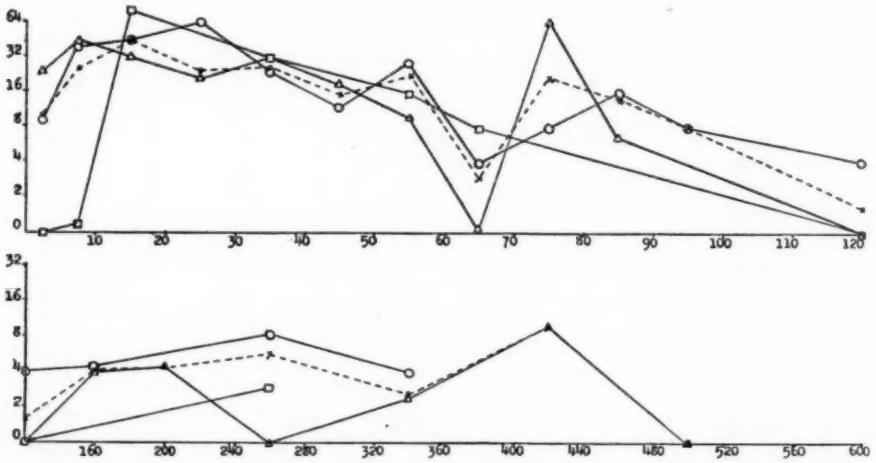

CHART 1. Size of infecting dose and average complement fixation titre.
□ = less than 1 mg. △ = ca. 1 mg. O = greater than 1 mg. X = total. The figures along the vertical line represent titres and along the horizontal line days after infection.

curve which differed from that of virulent strains in that it rose more slowly and did not reach so high a level. The route of administration of BCG differed from that of virulent strains but intravenous injection of BCG is generally considered to be a favorable route for antibody production (5, 6).

X-ray: The dogs had been followed by X-ray studies of the chest. Some of the X-ray films were made close enough in time to complement fixations in the same dog, so that the relation between the two could be studied. In the data used, complement fixations and films were made within two days of each other at zero to fourteen days, within six days at fifteen to forty-nine days, within ten days at fifty to ninety-nine days,

within twenty days at one hundred to one hundred ninety-nine, and fifty days at periods over two hundred days. Four X-ray classifications were used: (*1*) extensive density with no clearing, (*2*) density which is clearing, that is, the shadow has become smaller and less dense, (*3*) clear,

TABLE 3

Type of infection and average complement fixation titre

DAYS	PRIMARY	REINFECTION	BCG	AFTER BCG
0–4	1.5	44.0	0.0	14.9
5–9	4.8	160.0	2.0	31.0
10–19	27.3	74.0	4.5	20.8
20–29	21.4	44.5	6.4	32.0
30–39	16.0	20.5	9.0	26.0
40–49	12.5	18.0		0.0
50–59	17.0	28.0		6.3
60–69	4.0	5.0	Reinjection	32.0
70–79	8.0	8.0		
80–89	16.0	32.0		11.4
90–99		5.0		
100–139	0.6	5.0	4.3	
140–179	2.0	6.0	2.0	
180–219	5.3	2.0		
220–299	4.0	7.5		
300–379	2.9	6.5		
380–459	6.0			
460–539	0.0			
Difference from average for all samples	$n = 16$ $t = 2.02$ $P \cong 0.05$ $\bar{x} = -5.5$	$n = 15$ $t = 1.696$ $0.2 > P > 0.1$ $\bar{x} = +14.12$	$n = 4$ $t = 4.46$ $0.02 > P > 0.01$ $\bar{x} = -22.6$	$n = 8$ $t = 3.52$ $0.6 > P > 0.5$ $\bar{x} = -3.52$
Difference of primary from reinfection	$\bar{x} = 21.14$ $n = 15 \quad t = 1.94 \quad 0.1 > P > 0.05$			
Difference of primary from all samples in first 100 days	$n = 9$ $t = 3.54$ $P < 0.01$ $\bar{x} = -8.54$			

and (*4*) trace but no change. The last group was used because, at times, the density failed to clear entirely and there was left a shadow about 2 cm. in diameter which did not change over a long period. In the first group there were 34 observations on 23 dogs; in the second, 21 on 13; in the third, 11 on 15; and in the fourth, 8 on 6 dogs.

The results are presented in table 4 and chart 3. The number of observations is not great and there is no consistent difference between any two of the four groups.

Skin test: Skin tests have been done frequently on the dogs. Arbitrarily it was decided to compare skin test and complement fixation readings when they had been done within two days of each other in the first five days after infection (zero to four days), within five days at fifteen to ninety-nine days, and within twenty days at one hundred or more days. There were in addition many instances when skin tests had been done both before and after a complement fixation, and it seemed advantageous to include these data. Sometimes the skin reaction was of

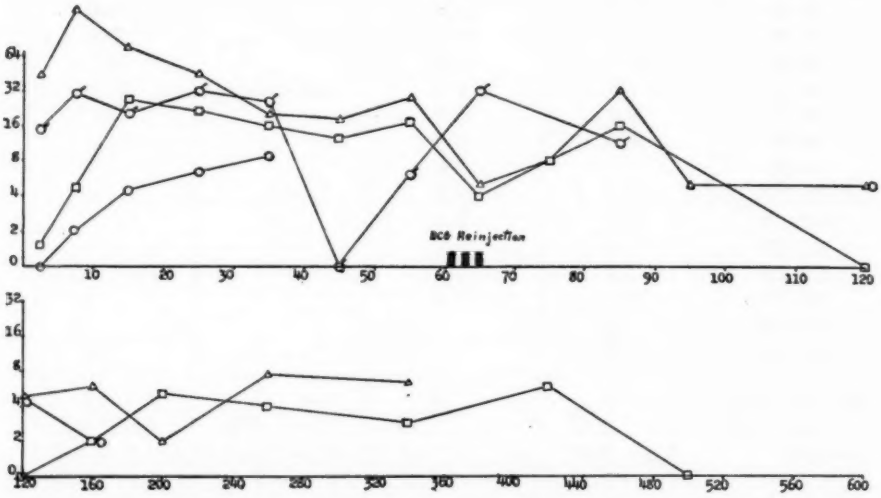

CHART 2. Type of infection and average complement fixation titre.
□ = primary. △ = reinfection. O = BCG. Ó = infection after BCG. The figures along the vertical line represent titres and along the horizontal line days after infection.

the same degree before and after the complement fixation, and in such instances it was assumed that the skin test grading would have been the same at the time of the complement fixation. Such a procedure was deemed reliable because skin test readings have been fairly constant. However, when there had been injection of tubercle bacilli between the two skin tests, the data were not included. Thus in table 5 the classifications "negative," "doubtful," 1+, 2+ and 3+ include not only observations on single skin tests and complement fixations, but also observations on skin tests which were the same before and after the

TABLE 4

X-ray classification and average complement fixation titre

DAYS	X-RAY CLASSIFICATION			
	Extensive	Clearing	Clear	Trace
0–4				
5–9	2.0		2.0	
10–19	22.2			
20–29	8.7			2.0
30–39	24.0	9.0	64.0	
40–49	6.0			16.0
50–59	18.0	20.3	6.7	
60–69	0.0	2.0	8.0	2.0
70–79		8.0		
80–89	16.0	14.3		8.0
90–99			8.0	
100–139	2.0		8.0	
140–179	8.0	6.0		4.0
180–219		0.0	16.0	
220–299	0.0			
300–379				3.7

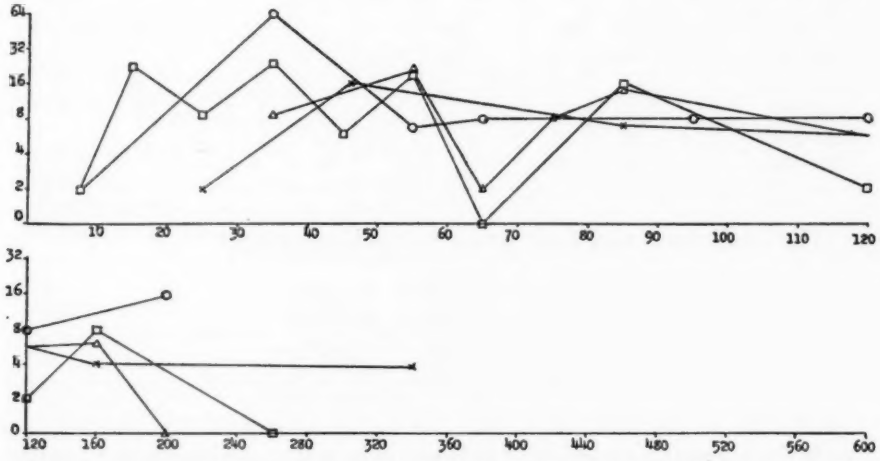

CHART 3. X-ray classification and average complement fixation titre.
□ = extensive. △ = clearing. O = clear. X = trace. The figures along the vertical line represent titres and along the horizontal line days after infection.

complement fixation. The classifications of table 5 in columns 7 to 13 describe the skin test at the two times it was observed. There were in all 101 observations on 42 dogs.

Examination of table 5 shows that higher complement fixation titres tend to be associated with higher skin test gradings. The correlation coefficient (product moment) of the association was determined. The effect of age of infection on the coefficient was calculated by the method of partial correlation. In this comparison, when two different skin tests had been used, the skin test reading at the time of the complement fixation was arbitrarily considered to be the average of the two skin test gradings. Doubtful skin tests were not included.

TABLE 5

Skin test to 1:100 OT and average complement fixation titre

DAYS	NEG.	1+	2+	3+	4+	NEG. TO 1+	1+ TO 2+	2+ TO 3+	3+ TO 4+	3+ TO 2+	2+ TO 1+	2+ TO NEG.	DOUBTFUL
0–4	8.3		20	80									
5–9		0	28.7								40		3
10–19			32.9	37.3		0		40					
20–29	5		9				32			8			
30–39			12	32				12	64	32			
40–49			6.7	32					64	4			
50–59	8		9	36				8.7	32	16			
60–79	4		6					2					
80–99			14	16		2			8		2	32	
100–139			3.7	8		0		2					
140–179			16			2					4		
180–219			8	2							0		
220–299		4	10	32				11		4			
300–399			0	8				0	8				

The coefficients and their levels of significance are:

$$r_{12} = +0.3330 \qquad P < 0.01$$
$$r_{23} = +0.3347 \qquad P < 0.01$$
$$r_{13} = -0.1684 \qquad P \cong 0.1$$
$$r_{12.3} = +0.4191 \qquad P < 0.01$$
$$N = 101$$

r_{12} is the correlation coefficient between skin test and complement fixation titre; r_{23}, titre and age of infection; r_{13}, skin test and age; $r_{12.3}$, the partial correlation coefficient of skin test and complement fixation titre holding age of infections constant. The first, second, and especially the fourth coefficients are of high significance, since a coefficient of 0.2540 corresponds to a P value of 0.01 for a sample of 101 observations.

The distribution of some of the variates was not normal. Since the

dilutions in the complement fixation tests were in geometric progression (1, 2, 4, 8, etc.) the end-titres were in a skew distribution. And since observations tended to be more frequent in the early days of the infection, the distribution of both complement fixations and skin tests at the time was also skew. However, the logarithms of these variates give an approximately normal distribution. Correlation of the logarithm to the base 10 of the complement fixation titre with the skin test reading gave a coefficient of 0.3966. Apparently then, the logarithmic distribution of

TABLE 6

Relationship of autopsy findings and complement fixation titres

PATHOLOGICAL FINDINGS	NUMBER OF DOGS	RATIO OF NUMBER OF TITRES 1:8 OR HIGHER TO NUMBER LESS THAN 1:8	AVERAGE TITRE
Main lesion			
Diameter of consolidation = 1–3 cm.	9	5/4	1:20
Diameter of consolidation = 3½–8 cm.	4	3/1	1:25
No acid-fast rods	8	5/3	1:8
Few acid-fast rods	3	3/0	1:32
Many acid-fast rods	3	1/2	1:13
Necrosis absent	6	2/4	1:14
Necrosis present	12	9/3	1:14
Pulmonary lymph nodes			
Negative	6	3/2	1:8
Tubercles present	10	8/2	1:23
Necrosis present	3	0/3	1:2
Liver			
Negative	4	2/2	1:12
Questionable foci present	4	2/2	1:12
Tubercles present	10	7/3	1:20

the variates gave only low values for coefficients and led to an underestimate of their significance.

Autopsy findings: The complement fixation titre was observed in 19 dogs which had died or were sacrificed within a few days of the date of their test. The following items in the postmortem findings were considered: in the principal lesion, diameter, presence of acid-fast bacilli and of microscopically proved necrosis; in the pulmonary lymph nodes, the presence of tubercles and of necrosis; in the liver, tubercles or other

definite evidence of tuberculosis. The antibody titre was studied according to each finding. The results are shown in table 6. An arithmetic average of titres has the disadvantage of being markedly influenced by even one high titre, especially where the numbers are few as they are here. Therefore, in order to show more clearly what portion of the titres were high, column 3 of table 6 presents the ratio of titres 1:8 or higher to those under 1:8. Examination of the table shows that in general as the lesion increases in severity the average titre increases or the number of high titres increases. Exceptions are met in the number of acid-fast rods and presence of necrosis in the regional lymph nodes. The count of acid-fast rods is influenced by the difficulty of the staining technique and suitable sampling, since the distribution is spotty. No explanation is offered for the fact that regional nodes showing necrosis were associated with lower titres than in the case of normal nodes, except that the number of dogs is small.

It would seem that these findings are not explainable by varying ages of the infection, since all but two of the infections were young (less than eighty-five days), and since in this group there was a slight relationship between titre and age of infection.

DISCUSSION

The lack of correlation of antibody titre with the size of infecting dose may be explained by two considerations. The dose may have been so large that a maximum titre was produced for that type of infection. Undoubtedly a sufficient decrease in dose would give a decrease in antibody titre. Or it may have been that the size of infecting dose bore an insignificant relationship to the resultant number of bacilli in the developed lesion.

The differences in titres with different types of infection might have been expected. Petit and Panisset (7) report a vigorous response in reinfected dogs. The differences between the titres of reinfection and infection with virulent bacilli after BCG are of interest.

The finding of the same antibody titres with different X-ray classifications might seem to be a conflict with findings in human tuberculosis. However, our experimental tuberculosis in dogs differs from the natural human disease in being less chronic, so that dogs tend to pass through the stages which have been described here with sufficient rapidity to make the classification less significant. Most of the animals used for this part of the study went through a period when their X-ray films showed

extensive lesions, clearing lesions, and clear lung fields; they varied in the length of time for which they remained in their classifications, but apparently did not vary enough to affect the antibody level.

The positive correlation of degree of reaction in the skin test with the antibody titre has not frequently been noted. Opie (8) noted a close correlation between hypersensitivity (Arthus phenomenon) and precipitin titre. The correlation was closest when he used a purified antigen (crystalline egg albumin). Culbertson (9), also using crystalline egg albumin, has found that the severity of the Arthus reaction in rabbits is directly correlated with the precipitating potency of the antiserum as determined by his neutralization technique. Freund, Casals-Ariet and Genghof (10) found such a positive correlation in rabbits injected with heat-killed tubercle bacilli in varying amounts of paraffin oil. The addition of paraffin oil to killed tubercle bacilli promotes both sensitization and antibody formation in rabbits (11). Also it has been noticed (6, 12, 13) that vaccinated animals maintain their skin sensitivity after they lose their complement-fixing antibodies, but that infected animals just before death tend to lose their skin sensitivity although the antibody titres remain more or less unaltered. It has been observed that when either BCG or heat-killed virulent bacilli are given by different routes there is little relationship between skin sensitivity and complement fixation titres. Intravenous injections give high antibody content and slight sensitivity, while subcutaneous and intracutaneous injections give lower antibody response and higher sensitivity. Clawson and Baker (13) desensitized 5 vaccinated rabbits by intravenous injection of heat-killed BCG, but the complement fixation and agglutinin titres increased. There is little evidence that the complement fixing antigen and the tuberculin antigen are identical; the antigens responsible for stimulation of complement-fixing antibodies and skin sensitivity need not be similar in solubility or antigenicity. The apparent explanation of our finding, a positive correlation of degree of skin test and complement-fixing antibody titre, is that pulmonary infections which were of the type that produce higher circulating antibody levels also producd greater skin sensitivity.

The true extent and severity of the lesions was not always shown in the antero-posterior X-ray films and therefore the titre of the serum was not so closely correlated with the X-ray findings as with the postmortem classification. Most of the dogs were classified successively in three of the four X-ray groups, but they varied in the length of the period during which they remained in each group.

SUMMARY

The complement fixation test was used for measuring antibody titres in experimental pulmonary tuberculosis in dogs.

Normal dogs showed only rarely a 4+ fixation in a titre of 1:2, or a 2 to 3+ fixation in a titre of 1:4. All tuberculous dogs showed an increase in titre, especially in the first forty to sixty days.

The sera of dogs given different infecting doses demonstrated no significant differences in average antibody level.

The various types of infection showed the following order from highest to lowest average titres: reinfections, infections with virulent strains after previous intravenous injection of BCG, primary infections and intravenous BCG.

Dogs exhibiting different types of X-ray pictures did not show different antibody levels.

A direct relationship between intensity of dermal reaction to tuberculin and height of antibody level was observed.

The sera of dogs with more severe lesions, as determined by autopsy studies, tended to show higher antibody titres.

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PSYCHOLOGICAL TESTING OF TUBERCULOUS PATIENTS[1,2]

The Intelligence, Occupational Preferences and Clerical Aptitudes of Tuberculous Patients with Reference to the Rehabilitation Program

IRVIN T. SHULTZ AND HARVEY RUSH

Any educational or rehabilitation program in a public sanatorium for the treatment of tuberculosis, such as Sunnyside Sanatorium near Indianapolis, Indiana, will obviously be aided by a knowledge of facts pertaining to the patient personnel. Not only are such facts essential from the point of view of directing the efforts of the individual patient, but they are also valuable from the point of view of comparisons with other groups of individuals in sanatoria or out. Educational diagnosis is as important psychologically as medical diagnosis is clinically. Both must be as complete and accurate as science can make them. The educator or applied psychologist has as great an opportunity in aiding the general rehabilitation program as does the attending physician and he should approach his problem with the same confidence and knowledge.

Intelligence ratings, for example, of groups of patients in different types of institutions for the treatment of tuberculosis should yield important clues for improvement in the administration, care and rehabilitation of the patients.

Another important step would be to find out something about the extent to which the past experiences of the patients and their present problems and illnesses have affected their motivation and interest in occupational matters. Many patients here have been confined for some time, so long as to have lost practically all touch with their former work. Others have pursued work unsuited to their mental and physical abilities. Others never have been established in earning their livelihood. Others have pursued a variety of occupations prior to their admission to the institution. It is important and valuable from the standpoint of guidance and rehabilitation to compare the occupational interests of a group thus institutionalized with a normal, outside group.

[1] From the Sunnyside Sanatorium, Indianapolis, Indiana.

[2] Publications, Indiana University, Psychological Clinic, Series II, Number 27.

Recent research has revealed that the old methods of selecting employees by age, years of experience, time spent in training and education or by intelligence rating were not as reliable as generally supposed. Specific abilities of various sorts often function independently, or do not correlate closely, with ability to do school work and often, too, they do not bear a high relationship to training and experience. To discover this innate ability, specific aptitude tests are necessary. In the general clerical field the Minnesota Clerical Test is more diagnostic and prognostic of clerical ability than high school diplomas, years of experience on the job or an intelligence rating.

Such a test is particularly useful because the field of general clerical work is especially suited, for several reasons, to the needs of a rehabilitation program. It is a rather wide field, offering a large number and variety of jobs. It is not physically strenuous. It normally is more remunerative than semiskilled labor. It does not necessarily require high intelligence or extensive education or even a high degree of training. Practically all of the training required can be offered to patients while undergoing treatment for tuberculosis. (Bookkeeping, shorthand, *etc.* can be taught to bed patients, and typing and business machine operations can be taught to ambulant patients.)

DESCRIPTION OF THE TESTS

The Pressey Senior Classification Test is composed of test items as follows: opposites, information, practical arithmetic and practical judgment, arranged in a cycle in order to facilitate scoring. The test is intended as a brief scale for measuring verbal intelligence or the ability to do school work. The directions are easily followed. Sixteen minutes are allowed for the completion of the test and the highest possible score is 96.

The Pressey Senior Verification Test is a checking test to be used following the Classification Test. It is an alternative form and organized in the same way and equated as to difficulty. Again sixteen minutes are allowed for completion, and 96 is the highest score a subject could achieve.

The Classification Test was given to 88 men and 101 women. After an interval of several days, the Verification Test was given to 77 of the 88 men and to 100 of the 101 women who took the Classification Test.

The author of the test gives tentative norms in terms of grades and ages: grades 7 to 12, ages eleven and one-half to seventeen and one-half. The test was intended for grade and section classification of grade and high school students, thus no norms were given by the author for the adult groups. Since the Sunnyside population is, with a few exceptions, adult, it was thought that

a more reliable and useful comparison might be made if the experimental group could be compared with another group of more nearly equal age, occupation and school achievement and one which was a more representative sample of the general population than grade and high school students.

Such a group was found described in a monograph entitled *A Manual of Selected Occupation Tests* (3). In this publication the authors describe the method of sampling and the statistical procedures involved in the study of the employed and unemployed working population of Minneapolis, St. Paul and Duluth, as found in the 1930 census. The reader is especially referred to the appendices of this manual for detailed information concerning the technique and adequacy of the sampled population to whom the Pressey Tests were given.

The Kuder Preference Record is designed to measure the amount of motivation that an individual displays, as judged by his reactions to the test material, in each of several fields of study or work. The test does not measure ability directly, but indicates to what extent the subject will be motivated to use whatever abilities he may possess, in other words, how much interest he shows for a given field or fields of occupation, as judged by his past experiences.

The individual is asked to answer such questions[3] as: whether he would prefer going to a movie or attending a symphony; going to an amusement park or playing a musical instrument at home. His choices when properly scored and totaled will thus reveal his interest in a given field. The author tentatively describes seven general fields of occupation: scientific, computational, musical, artistic, literary, social service and persuasive.

The scientific field includes such occupations as research scientist, chemist, physicist, inventor, geologist, psychologist, biologist, electrical engineer, laboratory technician, explorer.

The computational field covers such work as accountant, actuary, statistician, arithmetic teacher, purchasing agent, bond salesman, auditor, surveyor, architect.

In the musical field would be found such activities as singing or playing musical instruments, directing orchestra, band or chorus, composing and arranging, sound engineering, *etc.*

The artistic field would include artists, sculptors, cartoonists, photographers, architects, art critics, illustrators, *etc.*

In the literary field would be classified such activities as those of author,

[3] On the self-scoring form of the Record used in this study, subjects indicated their choice of one or two described activities presented in paired-comparison form, and numbered 1 and 2, respectively, by punching holes with a pin through either of two circles marked 1 and 2, respectively, corresponding to numbers of the alternative activities. Each pin prick pierced the score sheet for each of the 7 occupational fields and was scored as indicating interest in a given field, whenever it pierced one of a series of circles on the score sheet for that field.

journalist, editor, advertising copy writer, manuscript reader, proof reader, librarian, *etc.*

Social service is a rather broad and not very definite field of activities including occupations which involve primarily an interest in people and in aiding people, such as minister, missionary, social service case worker, nurse, vocational counselor, kindergarten teacher, church or club worker, personnel director, *etc.*

Persuasive occupations make up another broad field in which a prime requisite is the ability to influence and persuade others. It would include salesmen, many business executive positions, psychiatrists, buyers, lawyers, complaint adjusters, bill collectors, labor leaders, *etc.*

The test was originally devised for the educational and vocational guidance of high school and college students and has been standardized largely on groups of the latter classification.

A comparison was made between the groups upon which the author standardized his tests, hereafter known as the "standard group" and the Sunnyside patients, which will be referred to as the "test group". The Kuder Self-Scoring Occupational Preference Record (4) was given to 82 men and 108 women.

The Minnesota Clerical Test consists of two parts, name checking and number checking. The person taking the test must compare similar lists of digits and similar lists of names, checking those which are exactly alike. It is designed to be diagnostic and prognostic in that it differentiates a special ability to do general clerical work, independent of such factors as age (before forty), clerical experience and training, sex and intelligence.

The Minnesota Clerical Test was given to an unselected group of 65 men and 98 women patients at Sunnyside Sanatorium. The maximum age of the men was sixty-five, minimum fifteen, average, or mean age, 32.9; of the women the maximum age was fifty-three, minimum sixteen, average, or mean age, 28.1.

The Sunnyside group was compared with the employed and unemployed clerical workers described in the manual *Measured Characteristics of Clerical Workers* by Andrews and Paterson (5). The reader is referred to the manual for detailed description and analysis of the test, its construction, reliability and validity. This group will be known as the standard of the Minnesota group with which the Sunnyside group is compared.

These 3 tests were given to the patients of Sunnyside Tuberculosis Sanatorium during the academic year of 1939–40.

ANALYSIS OF THE RESULTS OF TESTS

The Pressey Tests: To what extent and in what manner does the population at Sunnyside compare with the sample group which will be designated as the Minnesota or standard group in intelligence?

Table 1 shows the number and per cent of Sunnyside men and women in each decile of the standard group, with reference to the Pressey Classification Test. An inspection of this table shows that 63, or 71.6 per cent, of the 88 men exceed the midpoint of the standard group, while 57, or 56.4 per cent, of the women exceed the midpoint of the standard group. The men thus achieve a higher ranking than the women and appear to be a group of higher ability level than the selected population used in the Minnesota study.

Table 2 shows a comparison of the scores of the patients on the Verification Test with the Minnesota, or standard group. Of the 77 men (these being of the same group taking the Classification Test) 56, or 72.7

TABLE 1

Pressey Senior Classification Test distribution of Sunnyside group by deciles of the Minnesota group

MEN			WOMEN		
Decile	Number	Per cent	Decile	Number	Per cent
10	12	13.6	10	3	3.0
9	16	18.2	9	11	10.9
8	13	14.8	8	15	14.9
7	12	13.6	7	16	15.8
6	10	11.4	6	12	11.9
5	6	6.8	5	14	13.9
4	5	5.7	4	6	5.9
3	7	8.0	3	10	9.9
2	5	6.0	2	6	5.9
1	2	2.3	1	6	7.9
Totals.....	88	100.0		101	100.0

per cent exceed the midpoint of the standard group. In the same manner, 100 women of the group taking the Classification Test, took the Verification Test with 55, or 55.0 per cent, exceeding the midpoint of the standard group.

Seidenfield (6) gave the Otis Self Administering Test of Mental Ability, Higher Form A, to 42 females and 62 males at the National Jewish Hospital at Denver, Colorado, a nonsectarian charitable institution for the treatment of tuberculosis. He concludes that his measured group conforms very closely to the norms given by Otis for his standard group.

The results here indicate that both men and women (men more so than women), on both the Senior Classification and Verification Tests,

rate somewhat higher in intelligence and ability to "get" school work than does the standard, or Minnesota group, of employed and unemployed adults. The Sunnyside group also shows this same general tendency when compared with the Seidenfield group.

The Kuder Test: The men and women at Sunnyside are only moderately motivated in terms of scientific interest. Seventy, or 36.8 per cent of the group, exceed the median score of the standard group as given by the author of the test. The men are considerably more interested in science than the women, 38, or 46.3 per cent, of the men as compared to only 32, or 29.6 per cent, of the women exceed the median score of the standard group.

TABLE 2

Pressey Senior Verification Test distribution of Sunnyside group by deciles of the Minnesota group

MEN			WOMEN		
Decile	Number	Per cent	Decile	Number	Per cent
10	11	14.3	10	5	5.0
9	14	18.2	9	4	4.0
8	13	16.9	8	10	10.0
7	7	9.1	7	12	12.0
6	11	14.3	6	14	14.0
5	9	11.7	5	15	15.0
4	4	5.2	4	5	5.0
3	4	5.2	3	11	11.0
2	4	5.2	2	4	4.0
1	0	00.0	1	10	10.0
Total.....	77	100.0		100	100.0

In the computational field 113, or 59.3 per cent, of the entire Sunnyside group exceed the median score of the standard group. Fifty-eight, or 68.3 per cent, of the men and 57, or 52.8 per cent, of the women rating above the standard median. Thus the men are definitely more interterested in this field than the women.

In music, the test group at Sunnyside expresses more interest than the standard group. One hundred and seven, or 56.3 per cent, of the sexes combined, 33, or 40.2 per cent, of the men and 74, or 68.5 per cent, of the women exceed the median score, with the women thus showing a greater preference than the men.

In artistic activities the interest trend of the test group is much the

same as in the musical field. One hundred and two, or 53.7 per cent, of the patients exceed the median score of the standard group. Men to the extent of 37, or 45.1 per cent, exceed the median score, while 65, or 60.2 per cent, of the women are so ranked. The women thus definitely outrank the men in artistic preference.

The least interest of all was displayed in the field of literary activity. Taking the men and women together, only 55, or 28.9 per cent, of them exceeded the standard group's median score. This total being made up of 17, or 20.7 per cent, of the men and 38, or 35.3 per cent of the women.

The social service field had the highest ranking of the seven fields in the test for the Sunnyside group, 120, or 63.2 per cent, of both men and women exceeding the standard median score, 39, or 47.6 per cent, of the men and 81, or 75.0 per cent, of the women.

The field of persuasive activity showed the greatest difference in the amount of interest displayed by men and women. Fifty-one men, 62.2 per cent, scored above the median. For the combined group the ranking is below that of the standard group, with but 78, or 41.1 per cent, exceeding the median score.

Discussion and Comment

Taken as a whole, the test group of Sunnyside patients has probably a considerably lower socio-economic background than the standard group and most certainly a much lower educational background. The standard group being all at least in the first year of college, while at least two-thirds of the test group have not finished high school and no more than 5 per cent have any education beyond high school grade.

It is probably rather surprising then, that the patients came as near as they did to the standard scores. Most of the marked variations from the standard can be accounted for by the conditions mentioned. The low preference of the test group for scientific and literary occupations very likely is the result of insufficient education to understand and appreciate these fields of work. On the other hand, many of the patients, particularly the women, have had some first-hand contact with the various social services and agencies and thus obtained a much livelier sense of the need of such work than would the college group, and hence might be naturally expected to show a greater than standard interest in this field. Furthermore, to the manual worker, who makes up a considerable percentage of the sanatorium population, office or clerical work would logically have a strong appeal because of his physical limitations.

The Minnesota Clerical Test: Table 3 shows the number, means, standard deviations and critical or difference ratios of the two groups on the Minnesota Clerical Test.

TABLE 3

Significant measures of Minnesota men and women workers and men and women patients at Sunnyside on the Minnesota Clerical Test

	NUMBER CHECKING TEST				NAME CHECKING TEST			
	Minnesota Men	Sunnyside Men	Minnesota Women	Sunnyside Women	Minnesota Men	Sunnyside Men	Minnesota Women	Sunnyside Women
Number	491	65	229	98	491	65	229	98
Mean	83.1	98.8	113.1	107.8	77.6	102.2	111.3	114.4
Standard deviation	29.2	31.8	30.8	26.4	34.3	35.8	36.5	32.8
Critical or difference ratio†		3.8		1.6*		5.2		.8

* Indicates difference in favor of Minnesota group. All other differences favored by Sunnyside group.

† Difference Ratios or Critical Ratios, *i. e.* the difference divided by the standard deviation of the difference is statistically reliable by standard formula if the difference is 3.0 or more between the groups. See Garrett, Statistics in Psychology and Education, 1937, New York, Longmans Green Company.

TABLE 4

Distribution of scores of Sunnyside patients for Minnesota Clerical Tests in deciles of Minnesota standard group

Decile	NUMBER CHECKING				NAME CHECKING			
	Men		Women		Men		Women	
	Number	Per cent	Number	Per cent	Number	Per cent	Number	Per cent
10	15	23.1	6	6.1	22	33.9	8	8.2
9	6	9.2	5	5.1	9	13.9	9	9.2
8	11	16.9	11	11.2	4	6.2	13	13.3
7	4	6.2	10	10.2	4	6.2	11	11.2
6	7	10.8	11	11.2	5	7.7	11	11.2
5	12	18.5	10	10.2	7	10.8	7	7.1
4	3	4.6	9	9.2	6	9.2	12	12.2
3	2	3.1	15	15.3	5	7.7	14	14.3
2	2	3.1	12	12.2	3	4.6	7	7.1
1	3	4.6	9	9.2	0	00.0	6	6.1
Total	65	100.0	98	100.0	65	100.0	98	100.0

An inspection of these ratios shows a difference greater than 3.0 in favor of the Sunnyside men over the standard group in both name

checking and number checking tests. This difference is somewhat greater on the name checking test. With reference to the Sunnyside women the critical ratio shows a small difference in favor of the Minnesota group on the number checking test and an even smaller difference in favor of the Sunnyside women in name checking test. These differences being so small they are not considered reliable, hence the two groups show like performance.

Table 4 indicates the same in per cents of overlapping, of scores of the Sunnyside men and women in deciles of the Minnesota standard group. The Sunnyside men exceed the median of the standard group 66.2 per cent on the number checking test, and 67.8 on the name checking test. The Sunnyside women, on the other hand, exceed the median of the standard group 43.9 per cent on number checking and 53.0 per cent on the name checking test. As a group, the men show a greater aptitude for this work than the women.

Since the factor of relative age is not important nor experience and training absolutely essential, it could be assumed that approximately half of the men and possibly not quite half of the women could be prepared for economic rehabilitation in this field by individual education.

SUMMARY AND CONCLUSIONS

1. The Sunnyside population is at least comparable to the general population in ability to do school work or in verbal intelligence.

2. The men at Sunnyside indicate a somewhat higher intelligence (ability to do academic work) than the women.

3. Men at Sunnyside show more preference than women for the computational, persuasive and scientific fields of occupation, in the order named. Women at Sunnyside show more preference than men for the social service, musical, artistic and literary fields, in the order named.

4. Both men and women patients combine to show the greatest interest in the field of social service, 63.2 per cent of them exceeding the median score of the standard group. Next is the computational field in which 59.3 per cent exceed the standard median, then musical (56.3 per cent), persuasive activities (41.1 per cent), scientific (36.8 per cent) and, finally, literary activities (28.9 per cent).

5. As a group, Sunnyside patients have evidently not allowed an average economic status, lack of education and accompanying social factors to discourage their occupational interests. These factors may,

on the other hand, actually have encouraged interest in some types of occupations.

6. Men and women patients at Sunnyside Tuberculosis Sanatorium compare very favorably with the standardized Minnesota employed and unemployed clerical workers. The men show significantly greater aptitude for this specialized ability than do the women.

7. These facts should be of interest to the rehabilitation program in general and to individual instruction in particular at Sunnyside, as well as to other sanatoria interested in rehabilitation and educational programs.

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Jessamine S. Whitney

1880-1941

A cloud hangs low over the National office. Jessamine Whitney's desk is vacant. None can yet realize that this is more than a brief pilgrimage nor doubt that tomorrow will be brightened by her return. This feeling may lighten today's sense of tragedy but cannot erase the deeper knowledge that our loss is without such compensation.

Miss Whitney was for twenty-two years statistician for the National Tuberculosis Association. The day before her death she was stricken with a heart attack in the offices of the Association.

Miss Whitney was an internationally known figure in the field of statistical research. Born in Norwich, New York, she received her A.B. degree from Cornell University in 1905, majoring in mathematics and economics. She also studied actuarial science at New York University. Because of her mathematical training, Miss Whitney was selected in 1909 by the United States Bureau of the Census to study the feasibility of compiling official life tables for this country. She taught in the public schools of Puerto Rico, and later became a special agent for the United States Bureau of Labor Statistics upon her return to the United States, and in this capacity made a study of the child labor conditions in cotton mills.

Prior to joining the National Tuberculosis Association in 1918, Miss Whitney acted as statistician for the United States Shipping Board. She was selected in 1929 as one of the eight American delegates to the International Conference on the Classification of Causes of Death, which met in Paris every ten years. Miss Whitney was the only woman appointed from any of the forty countries participating in the Conference. She was again a United States delegate to the same Conference in 1938. Miss Whitney was the author of many pamphlets and monographs on tuberculosis and public health work.

Eulogy brings scant comfort. She would not welcome it. Words possess no power to assuage our sorrow nor fill the emptiness in our hearts. The only eulogy that counts is our determination to cherish and foster in ourselves and in our Association the good things she has bequeathed.

Her wisdom, her judgment, her friendship, all these in some measure she has passed on to her colleagues.

It is for us to write Jessamine Whitney's eulogy in our daily lives that her years of devotion be not lost and that we preserve those qualities of hers that are eternal and that have made their contributions to our common labors.

Jessamine S. Whitney
1880-1941

Among all her bequests the most outstanding is her exemplification of the questioning mind. It is for such great souls as hers that William Blake penned the lines:

"The thirst to know and understand
A large and generous discontent
These are the gifts in life's rich hand
The things that are more excellent."

KENDALL EMERSON

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Tuberculosis in Ancient Egypt.—Archaeological and anatomical evidence clearly shows that tuberculosis afflicted the ancient communities of the Nile Valley at least as far back as the third millennium before Christ. At no period, perhaps, was it excessively frequent, though the lack of visceral remains available for study makes this point inconclusive. There is no evidence as to whether the human or the bovine type of bacillus was responsible for most of the lesions. The cow, however, was a common domesticated animal.—*The Evidence for the Incidence of Tuberculosis in Ancient Egypt, A. J. E. Cave, Brit. J. Tuberc., July, 1939, 33: 142.*—(*A. P.*)

Tuberculosis in Controlled Environment.—Patients in the Newark (N. Y.) State School for Mental Defectives have been given periodic examinations with tuberculin test and X-ray examination since January 1936. It was possible to divide the 2300 patients into two almost equal groups according to whether or not they were intimately exposed to open tuberculosis. The development of tuberculosis was observed in 25 patients during the period of observation. Each of these patients was in a ward in which open tuberculosis had been found; no instance of reinfection type tuberculosis developed among patients not intimately exposed. A marked drop in incidence was noted in the last twelve months of the study. This was presumably due to the construction of more adequate facilities for isolation. X-ray examination was given a group of 500 negative reactors as a check upon the accuracy of the tuberculin test. No significant tuberculous abnormalities were found. The authors point out that prolonged studies of this type should yield valuable information about the relative importance of endogenous and exogenous reinfection.—*Development of Tuberculosis in a Controlled Environment, R. E. Plunkett, G. W. Weber, W. Siegal & R. R. Donk, Am. J. Pub. Health, March, 1940, 30: 229.*—(*H. L. I.*)

Spread of Tuberculosis.—The incidence of tuberculous infection and disease among 539 white and 686 colored children less than fifteen years of age from 138 white and 147 colored households harboring one or more cases of sputum-positive or fatal cases of tuberculosis was studied. The results were compared with those obtained from a study of 81 white and 78 colored children from 19 white and 18 colored households harboring either a sputum-negative or sputum-doubtful case of tuberculosis. The results of the intracutaneous tuberculin test indicated that under like intrafamilial exposure there is a great similarity in the incidence of infection among the two races. Among those exposed to sputum-positive cases of tuberculosis a positive reaction to 1.0 mg. or less of Old Tuberculin was obtained in 71 per cent of those ranging in age from one to four years, while among those five to nine years and ten to fourteen years of age 82 and 84 per cent respectively reacted. Among those less than one year of age 28 per cent were tuberculin-